IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Hogan		
Serial No.:	09/613,887	Group No.:	1634
Filed:	07/11/2000	Examiner:	Goldberg
Entitled:	**METHODS AND COMPOSITIONS FOR PERIOPERATIVE GENOMIC PROFILING**		

CORRECTED APPELLANT'S BRIEF

APPEAL NO.:

EFS Web Filed
Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Dated: **August 27, 2009** By: /Thomas P. Vita, Jr./
Thomas P. Vita, Jr.

This Corrected Appellant's Brief is in furtherance of the Notice of Appeal filed October 31, 2008, and is in response to the Notification of Non-Compliant Appeal Brief mailed July 28, 2009. The Brief has been corrected in accord with 37 CFR § 41.37 to include: a statement of the status of the claims on appeal; references in the summary of the claimed subject matter to claims 106, 127, 135, 143, 144, 140, 186, and 189; a clean copy of the appealed claims; and statements setting forth where in the record the evidence was entered by the examiner.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. HOGAN-04448. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is the Inventor, Kirk Hogan, Madison, WI.

II. RELATED APPEALS AND INTERFERENCES

In an Appeal Brief filed September 19, 2005 in the present matter (Application Serial No. 09/613,887) the Appellant appealed the Final Office Action date January 11, 2005 (Appeal No. 2006-1560). A copy of the Decision on Appeal mailed July 25, 2006 is included in the RELATED PROCEEDINGS APPENDIX. Co-pending U.S. Application Serial No. 09/976,423, a continuation-in-part of the present application, was the subject of Appeal No. 2006-1517. A copy of the Decision on Appeal mailed July 31, 2006 is included in the RELATED PROCEEDINGS APPENDIX. Co-pending U.S. Application Serial No. 09/976,423 is the subject of an Appeal Brief filed April 15, 2009 appealing the Final Office Action dated March 24, 2008.

III. STATUS OF CLAIMS

Claims 106-125 and 127-191 have been rejected and are currently under appeal.

Claims 1-20 were filed in the original application. During prosecution of the application, claims 1-20 were cancelled and claims 21-41 were added in the Amendment and Response to Office Action filed August 9, 2001. Claims 21-41 were cancelled and claims 42-73 were added in the Amendment and Response to Final Office Action filed January 14, 2003. Claims 42-73 were cancelled and claims 74-105 were added in the Amendment and Response to Office Action filed January 5, 2004. Claims 74-105 were rejected in the Final Office Action dated January 11, 2005.

In an Appeal Brief filed September 19, 2005 the Appellant appealed the Final Office Action of January 11, 2005. In the Decision on Appeal mailed July 25, 2006 the Board of Patent Appeals and Interferences affirmed the rejection. Claims 74-105 were cancelled and claims 106-191 were added in an Amendment and Request for Continued Examination after Board Decision filed September 25, 2006. Claim 126 was cancelled in the Amendment and Response to Final Office Action of December 11, 2006. No other claims are pending. Therefore, claims 106-125 and 127-191 are pending in the application.

Appellant appeals the Final Office Action of May 21, 2008.

The Claims, as they now stand, are set forth in Section VIII. CLAIMS APPENDIX.

IV. STATUS OF AMENDMENTS

All previous amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to methods for perioperative genomic screening of surgical subjects, in particular to perioperative screening for nucleic acid genetic markers indicative of responses to anesthesia, and to other perioperative or operative treatments and procedures. In current clinical practice, there is no technology available that provides the information of the perioperative genomic profiles of the present invention. In the past, screening tests of a patient's phenotype (*e.g.*, blood cell count and chemistries, urinalysis, electrocardiogram (EKG), and chest X-ray) were routinely performed prior to surgery. However, the present-day procedure for screening for susceptibility to heritable disorders of consequence in the interval surrounding surgery does not look at nucleic acid genetic markers, and is limited to asking a patient if they or their family members have had any previous difficulties with anesthesia or surgery. The use of laboratory phenotypic tests for patients prior to surgery has generally been reduced or eliminated. Reasons for elimination include the inaccuracy and lack of specificity of the various phenotypic tests, the aggregate costs of many different kinds of phenotypic screening tests necessary to assemble test panels, and uncertainty as to how to alter treatment course of action in response to phenotypic test results. Accordingly, contemporary anesthesiology and surgery textbooks emphasize that recent studies indicate a lack of benefit from phenotypic testing as a method of assessing patients before surgery, and stress that cost-benefit strategies can only be justified when laboratory testing is reduced to that indicated by history-taking.

The perioperative genomic profiles of the present invention stand in direct contrast to the panels of phenotypic tests currently available and previously used. In the present invention, genetic alleles are tested in ensemble according to selection categories and criteria taught by the present invention, in order to construct a personalized perioperative genomic profile. The perioperative genomic profiles of the present invention may be used, for example, to select the safest and most effective anesthetic regimen and surgical procedure, and to begin life-saving interventions as soon as possible. The perioperative genomic profiles of the present invention thereby solve many of the problems described above that have led practitioners away from

preoperative phenotypic testing. The perioperative genomic profiles of the present invention are cost and time effective. As taught by the present invention, genomic markers are selected for inclusion in the profile by virtue of their analytical validity (*i.e.*, a high level of accuracy, specificity, and predictive value), clinical validity (*i.e.*, a high level of correlation between DNA sequence variation and the trait of interest) and clinical utility (*i.e.*, a significant impact of the test result on the patient's well-being during and after surgery). The perioperative genomic profiles of the present invention thus allow for the individualization of treatment options for each subject undergoing a surgical procedure. In this fashion, the present invention provides a novel diagnostic tool currently unavailable in the surgical field, enabling solutions for problems that have no available alternatives. In the absence of any competing technology for quantifying subject's genetic contributors to perioperative risk, the present invention provides life- and cost-saving information to caregivers on an accelerated and amplified scale relative to current diagnostics.

With respect to claim 106, in one embodiment of the present invention, a method is described wherein a patient is screened perioperatively to determine a risk for complications during a surgical procedure (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22, line 8) associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic data", page 25, lines 19-25, and page 26, line 9 – page 27, line 14), comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, subjecting the sample to an assay (described, for example, at page 24, line 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26 line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5), in two or more genes associated with two or more conditions to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22), selecting a perioperative course of action based on information from the genomic profile (Figure 1, "Alter Intervention"), wherein the

subjecting step occurs after the patient is scheduled for surgery, but before completion of the surgical procedure, thereby determining a risk for complications (described, for example, at page 1, line 10 – page 3, line 4, and page 21, line 28 – page 22, line 8) during the surgical procedure, and performing the surgical procedure wherein the perioperative course of action is used by at least one of the group of an anesthesiologist (described, for example, at page 43, line 10), a nurse (described, for example, a page 22, line 11) and a surgeon (described, for example, at page 43, line 10). In some embodiments, the surgical procedure is the first surgical procedure (described, for example, at page 3, lines 21-23) for the subject. In other embodiments, previous surgical procedures on the patient have been with one or more complications (described, for example, at page 1, lines 10-15). In some embodiments the course of action comprises administration of anesthesia during a surgical procedure (described, for example, at page 4, lines 23-25, page 21, lines 28-29, and page 33, line 15 - page 34, line 14). In further embodiments, the anesthesia is general anesthesia (described, for example, at page 3, line 20, and page 23, lines 1-5). In other embodiments, the general anesthesia is inhalational anesthesia (described, for example, at page 23, lines 1-5). In another embodiment, the general anesthesia is intravenous anesthesia (described, for example, at page 23, lines 1-5). In some embodiments, the anesthesia is regional anesthesia (described, for example, at page 22, lines 25-30). In other embodiments, the regional anesthesia is spinal or epidural anesthesia (described, for example, at page 22, lines 25-30). In other embodiments, the surgical procedure is non-invasive surgery (described, for example, at page 3, lines 22-23, and page 22 lines 12-13). In another embodiment, the surgical procedure is invasive surgery (described, for example, at page 3, line 22, and page 22, lines 13- 17). In yet another embodiment, the course of action comprises administration of anesthesia during a medical procedure (described, for example, at page 4, lines 4- 10). In a further embodiment, the genomic profile comprises information pertaining to a pharmacodynamic risk (described, for example, at page 3, lines 24-25, page 4, lines 25-26, page 23, lines 13-17, and page 29, lines 6-10). In still further embodiments, the genomic profile comprises information pertaining to a pharmacokinetic risk (described, for example, at page 3, lines 25-26, page 4, lines 26-27, page 23, lines 13-17, and page 26, lines 10 – 14). In another embodiment, the genomic profile of the present invention comprises presymptomatic diagnosis (described, for example, at page 3, lines 26-27, and page 4, lines 27-28). In additional embodiments the genomic profile comprises information pertaining to differential diagnosis of co-existing diseases (described, for example,

at page 3, lines 26-28, page 4, lines 28-29, page 7, lines 2-4, page 23, lines 25-19, page 29, lines 15-20, page 31, line 25 – page 33, line 3, and page 33, lines 4-14). In some embodiments the two or more nucleic acid genetic markers comprise mutations in two or more genes, wherein the genes are selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2, F5*, *RYR1*, *CACNA1S*, and *CPT2* (described, for example, at page 4, lines 1-3, and page 4, lines 18-19). In some embodiments the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments the two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example, at page 28, lines 9-10). In other embodiments, the genomic profile consist of alleles in genes encoding BChE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, and CPT2 (described, for example, at page 4, lines 1-3, and page 4, lines 18-19).

With respect to claim 127, in one embodiment of the present invention, a method is described for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21, line 28 – page 22 line 8) during a surgical procedure associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26, line 9 – page 27 line 14) comprising providing a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject, wherein the perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and example, page 46 lines 22-25), is a patient scheduled for a surgical procedure and has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5) in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22), selecting a surgical treatment course of action based on information from the genomic profile (described, for example, at page 7, lines 6-7, page 23, lines 2-4, and page 26, lines 24-26), and subjecting the subject to a surgical

procedure. In some embodiments, the genetic markers are associated with a pharmacological response (described, for example, at page 4, lines 11-13). In other embodiments, the pharmacological response is to an anesthetic (described, for example, at page 4, lines 15-16). In other embodiments the pharmacological response is to drugs used in anesthetic practice (described, for example, at page 4, lines 11-16). In a further embodiment, the two or more nucleic acid genetic markers comprise a mutation in two or more genes associated with two or more conditions, wherein the genes are selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2* (described, for example, at page 4, lines 1-3, and page 4, lines 18-19). In some embodiments, the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments, the two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example, at page 28, lines 9-10). In other embodiments, the genomic profile consists of alleles in genes encoding BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2 (described, for example, at page 4, lines 1-3, and page 4, lines 18-19).

With respect to claim 135, in one embodiment of the present invention, a method is described of screening a patient perioperatively to determine a risk for complications during a surgical procedure (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22 line 8) from known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26, line 9 – page 27, line 14) comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and experimental example page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5), "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and page 46, line 26 – page 47, line 25) for detecting genetic markers in genes clinically associated with conditions selected from the group consisting of butyrylcholinesterase deficiency (described, for example, at page 2, lines 9-16, page 30, line 24 - page 31, line 2, and Table 1, page 48), impaired debrisoquine metabolism (described, for example, at page 2, lines 17-21, page 31, lines 3-9, and Table 2, page 48), sepsis (described, for example, at page 2, line 23 – page 3, line 4),

thrombosis (described, for example, at page 6, line 24, page 32, lines 5 – 18, and Table 3, page 48), and malignant hyperthermia (described, for example, at page 1, line 25 -page 2, line 4, page 31, lines 14-24, and Table 4, page 49) to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, line 6-10, and page 24, line 21-22), directing a physician to a perioperative treatment course of action based on information from the genomic profile for determining a risk for complications during a surgical procedure (described, for example, at Figure 1, "Alter Intervention" and Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data"), and subjecting the subject to a surgical procedure. In one embodiment, the physician is an anesthesiologist (described, for example, at page 43, line 10). In further embodiments, the course of action comprises administration of anesthesia during a surgical procedure (described, for example, at page 4, lines 23-25, page 21, lines 28-29), and page 33, line 15 - page 34, line 14). In other embodiments, the physician is a surgeon (described, for example, at page 43, line 10). In some embodiments, the surgical procedure is non-invasive surgery (described, for example, at page 3, lines 22-23, and page 22 lines 12-13). In another embodiment, the surgical procedure is invasive surgery (described, for example, at page 3, line 22, and page 22, lines 13- 17). In some embodiments, the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments, the two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example, at page 28, lines 9-10).

With respect to claim 143, in one embodiment of the present invention, a method is described of screening a patient perioperatively to determine a risk for complications during a surgical procedure (described in the Specification, for example, at page 1, line 10 – page 3, line 4, and page 21, lines 28 – page 22, line 8) from known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26, line 9 – page 27 line 14), comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and

page 46, line 26 – page 47, line 25), for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency (described, for example, at page 2, lines 9-16, page 30, line 24 - page 31, line 2, and Table 1, page 48), and impaired debrisoquine metabolism (described, for example, at page 2, lines 17-21, page 31, lines 3-9, and Table 2, page 48), to generate a genomic profile (described, for example, at page 3, line 17, Figure 1 "Genomic Profile", page 23, lines 6-10, page 24, lines 21-22), directing a physician to a perioperative treatment course of action based on information from the genomic profile for determining a risk for complications during a surgical procedure (described, for example, at Figure 1, "Alter Intervention" and Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data"), and subjecting the subject to a surgical procedure.

With respect to claim 144, in one embodiment of the present invention, a method is described for selecting an appropriate anesthesia treatment during surgery (described in the Specification, for example, at page 2 line 23 - page 3, line 4, page 3, line18, and page 22, line 18 – page 23, line 5), comprising providing a sample (described, for example at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5), "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and page 46, line 26 – page 47, line 25), that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein the markers are known to be associated with adverse responses to anesthesia treatment (described, for example, at page 6, lines 19-24, and page 30, lines 15-20), and subjecting the subject to a surgical procedure, wherein the assay results are consulted by a physician in selecting an appropriate anesthesia treatment for the subject based on information from the assay results (described, for example, at Figure 1, "Alter Intervention"). In one embodiment, the physician is an anesthesiologist (described, for example, at page 43, line 10). In one embodiment, the selecting step comprises selection of dosages of anesthesia (described, for example, at page 1, line 17, and page 2, lines 20-21). In another embodiment, the selecting step comprises selection of anesthesia compounds (described, for example, at page 1, line 17, page 28, lines 17-19,

and page 47, line 27). In a further embodiment, the selecting step comprises selection of monitoring procedures (described, for example, at page 7, lines 7-12, and page 47, line 27).

With respect to claim 149, in one embodiment of the present invention, a method is described providing a perioperative course of action to a clinician based on a patient's risk for complications (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22, line 8) during and after a surgical procedure associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic data", page 25, lines 19-25, and page 26, line 9 – page 27, line 14), comprising obtaining consent from a patient to obtain and assay a sample from a perioperative subject for genetic variations (described, for example, at page 46, lines 13-21), the patient being a patient scheduled for a surgical procedure that has not yet completed the surgical procedure (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and page 46 lines 22-25), obtaining the sample from the patient (described, for example at page 24, line 23 - page 25, line 2), forwarding the sample to a clinical laboratory (described, for example, at page 6, lines 6-8), isolating DNA from the sample in a clinical laboratory (described, for example, at page 46, lines 22-25), subjecting the DNA to an assay (described, for example, at page 24, line 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26 line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and example page 46, line 26 – page 47, line 25) in the clinical laboratory for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5), in two or more genes associated with two or more conditions to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22) wherein the subjecting step occurs after the patient is scheduled for surgery but before completion of the surgical procedure, forwarding the results of the genomic profile to the clinician (described, for example, at Figure 1 "M.D. User Interpretation"), directing the clinician to a perioperative treatment course of action for the patient based on the risk for complications during and after the surgical procedure (described, for example, at Figure 1, "Alter Intervention", and Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data") based on information from the genomic profile (described, for example, at page 7, lines 6-7, page 23, lines 2-4, and page 26, lines 24-26), subjecting the patient to a surgical procedure based on the perioperative course of action, distributing the results of the patient's genomic profile according to the patient's preference wherein the distributing is selected from the

group consisting of destroying the results, saving the results for future access by the patient, saving the results for future access by the clinician, and donating the results for research (described, for example, at Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data" and at page 45, lines 1-13), and distributing the patient's sample according to the patient's preference wherein the distributing is selected from the group consisting of destroying the sample, saving the sample for future access, and donating the sample for research (described, for example, at page 45, lines 1-13). In some embodiments, the directing the clinician to the perioperative course of action comprises a computer program comprising instructions which direct a processor to analyze the results of the genomic profile (described, for example, at page 42, lines 5-11 and page 43, line 29 – page 44, line 2). In other embodiments, the instructions translate results into information of predictive value for a clinician (described, for example, at page 45, lines 17-19). In further embodiments, the instructions translate the results into a risk assessment for treatment options (described, for example, at page 44, lines 4-6). In another embodiment, the instructions translate the results into recommendations for treatment options (described, for example, at page 44, lines 4-6). In a further embodiment, the instructions generate a report for display to a clinician (described, for example, at page 44, lines 6-9). In other embodiments, the instructions generate a report for display to a clinician (described, for example, at page 44, lines 6-9). In some embodiments, the display is in the form of a report that can be printed (described, for example, at page 44, lines 6-9). In other embodiments, the display is in the form of a report on a computer monitor (described, for example, at page 44, lines 6-9). In another embodiment, the instructions are sufficient to receive, process and transmit the results of the genomic profile to and from the patient, a clinical laboratory and medical personnel (described, for example, at page 44, lines 22-24). In some embodiments, the transmission of the results uses an electronic communication system (described, for example, at page 44, lines 27-28). In other embodiments, the electronic communication system transmits the results to a distant computer system for processing (described, for example, at page 44, lines 15-17). In further embodiments, the instructions comprise information to optimize perioperative care that, based on at least the presence of variant alleles of two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNF*α,(described, for example, at page 4, lines 1-3, and page 4, lines 18-19) directs the clinician to a specific perioperative clinical pathway for said patient (described, for example, at page 4, lines 20-24). In some embodiments, the perioperative course of action is an anesthesia treatment course of

action (described, for example, at page 4, lines 23-25, page 21, lines 28-29, and page 33, line 15 - page 34, line 14). In further embodiments, the anesthesia treatment course of action is a general anesthesia course of action (described, for example, at page 3, line 20, and page 23, lines 1-5). In other embodiments, the general anesthesia treatment course of action is n inhalational anesthesia treatment course of action (described, for example, at page 23, lines 1-5). In another embodiment, the general anesthesia treatment course of action is n intravenous anesthesia treatment course of action (described, for example, at page 23, lines 1-5). In other embodiments, the general anesthesia treatment course of action is a combined inhalational and intravenous anesthesia treatment course of action (described, for example, at page 23, lines 1-5). In some embodiments, the anesthesia treatment course of action is a regional anesthesia treatment course of action (described, for example, at page 22, lines 25-30). In further embodiments, the anesthesia treatment course of action is a combined regional and general anesthesia treatment course of action (described, for example, at page 23, lines 1-5 and at page 22, lines 25-30). In some embodiments, the perioperative treatment course of action is an anesthesia course of action during a medical procedure (described, for example, at page 4, lines 4- 10). In still further embodiments, the perioperative treatment course of action comprises selection of dosages of analgesic compounds (described, for example, at page 6, lines 26-28, and page 31, lines 3-9). In another embodiment, the selection comprises increasing the dosage of analgesic compounds metabolized by CYP2D6 (page 31, lines 3-9). In yet another embodiment, the selection comprises decreasing the dosage of analgesic compounds metabolized by CYP2D6 (page 31, lines 3-9). In some embodiments, the perioperative treatment course of action comprises prophylaxis for thrombosis (described, for example, at page 32, lines 5-18). In other embodiments, the prophylaxis comprises increasing prophylaxis for thrombosis associated with variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS* (described, for example, at page 32, lines 5-18). In further embodiments, the prophylaxis comprises decreasing prophylaxis for thrombosis associated with variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS* (described, for example, at page 32, lines 5-18). In some embodiments, the perioperative course of action comprises monitoring procedures (described, for example, at page 7, lines 7-12, and page 47, line 27). In other embodiments, the perioperative course of action comprises pre-operative phenotypic tests and consultations (described, for example, at page 5, lines 21-22, and page 22, lines 2-3). In further embodiments, the risk of complications provides a prognosis after an anesthesia treatment course of action (described, for example, at page 7, lines 5-6).

In another embodiment, the perioperative course of action is a surgical treatment course of action (described, for example, at page 7, lines 6-7, page 23, lines 2-4, and page 26, lines 24-26). In further embodiments, the surgical treatment course of action is a non-invasive surgical treatment course of action (described, for example, at page 3, lines 22-23, and page 22 lines 12-13). In another embodiment, the surgical treatment course of action is n invasive surgical treatment course of action (described, for example, at page 3, line 22, and page 22, lines 13- 17). In other embodiments, the risk of complications provides a prognosis after a surgical treatment course of action (described, for example, at page 7, lines 5-6). In some embodiments, the perioperative treatment course of action comprises a post-operative treatment course of action (described, for example, at page 2, lines 23-26, page 3, lines 1-2, and page 6, lines 23-24). In one embodiment, the perioperative treatment course of action directs a clinician to a specific clinical pathway of medical intervention for the patient (described, for example, at page 7, lines 2-4 and lines 10-12, and section I.D. "Applications and Interventions of Specific Markers" page 30, line 14 – page 34, line 14). In other embodiments, the perioperative treatment course of action directs a clinician to a specific clinical pathway of anesthesia intervention for said patient (described, for example at page 30, line 14 – page 34, line 14). In another embodiment, the assay comprises structure-specific cleavage of oligonucleotide probes assay (described, for example, at page 47, lines 4-22). In some embodiments, the present invention further comprises encrypting the results of the genomic profile with privacy security protocols (described, for example, at page 44, lines 22-27). In other embodiments, the present invention further comprises decoding the results of the genomic profile with privacy security protocols (described, for example, at page 44, lines 22-27).

With respect to claim 186, in some embodiments, the subjecting the DNA to an assay further comprises providing a kit for generating a perioperative genomic profile for a subject (described, for example, at page 34, lines 21-23), comprising reagents configured such that when exposed to a sample containing target nucleic acid (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNF*α (described, for example, at page 4, lines 1-3, and page 4, lines 18-19) so

as to generate a genomic profile for use in selecting a perioperative course of action for the subject, and a computer program on a computer readable medium comprising instructions which direct a processor to analyze data derived from use of the reagents (described, for example, at page 42, lines 5-11 and page 43, line 29 – page 44, line 2), and generating the genomic profile with the kit.

With respect to claim 189, in one embodiment of the present invention, a method is described wherein a patient is screened perioperatively to determine a risk for complications during a surgical procedure (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22, line 8) associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic data", page 25, lines 19-25, and page 26, line 9 – page 27, line 14), comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, subjecting the sample to an assay (described, for example, at page 24, line 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26 line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5), in two or more genes associated with two or more conditions to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22) wherein the marker are selected by the criteria of analytical validity, clinical validity and clinical utility (described, for example, at page 27, lines 19-20), selecting a perioperative course of action based on information from the genomic profile (Figure 1, "Alter Intervention"), wherein the subjecting step occurs after the patient is scheduled for surgery, but before completion of the surgical procedure, thereby determining a risk for complications (described, for example, at page 1, line 10 – page 3, line 4, and page 21, line 28 – page 22, line 8) during the surgical procedure, distributing the results of the patient's genomic profile according to the patient's preference wherein the distributing is selected from the group consisting of destroying the results, saving the results for future access by the patient, saving the results for future access by the clinician, and donating the results for

research (described, for example, at Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data" and at page 45, lines 1-13), and distributing the patient's sample according to the patient's preference wherein the distributing is selected from the group consisting of destroying the sample, saving the sample for future access, and donating the sample for research (described, for example at at page 45, lines 1-13). In some embodiments, the selecting of markers, the subjecting the sample to the assay, and the distributing of the results of the patient's genomic profile is organized by an integrated electronic system (described, for example, at page 7, lines 19-22). In other embodiments, the present invention further comprises selecting the genetic markers from the group consisting of genetic markers of pharmacogenetic risk (described, for example, at page 29, lines 5-6) genetic markers of co-existing symptomatic conditions (described for example, at page 3, lines 27-29), genetic markers of co-existing non-symptomatic conditions (described, for example, at page 3 lines 26-27, genetic markers of outcomes of a surgical procedure (described, for example, at page 30, lines 3-5), genetic markers of a patient in a specific group (described, for example, at page 30, lines 5-12), genetic markers that predict postoperative outcomes (described, for example, at page 30, lines 3-5), and genetic markers consisting of unique genomic identifiers (described, for example, at page 30, lines 9-13).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are four grounds of rejection to be reviewed on appeal:

Ground of Rejection 1 – Whether claims 106 – 124, 127-133, 135-150, 161-186, 189 and 191 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia").

Ground of Rejection 2 – Whether claims 151-160, 187-188, and 190 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia") as applied to claims 106 – 124, 127-133, 135-150, 161-186, 189 and 191 above, and further in view of Lapointe *et al.* (US 6,678,669, January, 2004) (hereinafter "LaPointe").

Ground of Rejection 3 – Whether Claim 185 is obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular

Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia") as applied to claims 106 – 124, 127-133, 135-150, 161-186, 189 and 191 above, and further in view of Lyamichev *et al.* (Nature Biotechnology, Vol. 17, pages 292-296, March, 1999) (hereinafter "Lyamichev").

Ground of Rejection 4 – Whether claims 125 and 134 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia") as applied to claims 106 – 124, 127-133, 135-150, 161-186, 189 and 191 above, and further in view of the specification (Tables 1-4).

VII. ARGUMENT

VII.A. Ground of Rejection 1 - Whether claims 106 – 124, 127-133, 135-150, 161-186, 189 and 191 are obvious over Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia.

The factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 35 U.S.C. are summarized as follows:

1. Determining the scope and contents of the prior art
2. Ascertaining differences between the prior art and the claims at issue
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying "a **reason** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd., 06-1329, slip op. (Fed. Cir. June 28, 2007)*, at 13-14 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added).

Simple knowledge of a problem is not sufficient motivation. The Federal Circuit has recently asserted: "knowledge of a problem and motivation to solve it **are entirely different** from motivation to combine particular references to reach the claimed method. *Innogenetics*, slip op. at 14 ("A generalized motivation to develop a method **is not** the kind of motivation required by the patent laws.")". *Innogenetics NV v. Abbott Labs.,* 512 F.3d 1363 at 1373 (Fed. Cir. 2008) (emphasis added). Clearly, mere identification of a problem in prior art is not enough to provide the motivation to invent. As well, the *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. Each

element of obviousness must be supported by substantial evidence, and must meet or exceed a preponderance of evidence burden. See M.P.E.P. 2144.

The Appellant submits that the Office has failed to establish a prima facie case of obviousness because: 1) the Office has erred in resolving the level of ordinary skill in the pertinent art; 2) the Office has not provided a motivation to combine the references; 3) the cited references do not teach or suggest all elements of the presently claimed invention; and 4) the Office has erred in determining the scope and contents of the prior art and in ascertaining differences between the prior art and the claims at issue. Even if a prima facie case of evidence had been established, the Appellant has provided more than sufficient evidence to counter such a showing.

VII.A.1. The Office has erred in resolving the level of ordinary skill in the pertinent art

In the Final Office Action of May 21, 2008 the Office makes numerous speculations regarding what an ordinary artisan would or would not have recognized, and what an ordinary artisan would or would not have been motivated to do. See, for example:

> "The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics." (Final Office Action of May 21, 2008 pages 7- 8.)

> And:

> "The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis." (Final Office Action of May 21, page 8.)

> Despite these assertions, the Office has never provided any evidence of any kind to back

up the Office's speculations. Similarly, despite the Appellant's multiple invitations to provide such evidence during prosecution of the present application, in the Final Office Action of May 21, 2008 the Office fails once again to do so.

The Appellant notes that the Office correctly identifies one of ordinary skill in the art as a clinician. Moreover, the Office expressly recognizes an anesthesiologist as one of ordinary skill in the art:

> "Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture or the patient's genetic make-up." (Final Office Action of May 21, 2008, page 10.) (Emphasis added.)

And:

> "The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions." The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Final Office Action of May 21, 2008, page 9.) (Emphasis added.)

However, the Appellant notes that at the time the invention was made, ordinary anesthesiologists or other perioperative clinicians were not familiar with, and would not and did not look to the Office's non-analogous molecular biology references. Accordingly, the Appellant submits that the Office's speculations and conclusory statements regarding the motivation and common sense of the ordinary artisan anesthesiologist to combine the claim elements to yield the claimed invention are unsupported by proper evidence, and are in error.

In turn, the Appellant has provided factual evidence that the Office has never met its duty to establish a *prima facie* case of obviousness in the first instance. For example, the Second Declaration of Kirk Hogan, M.D. under 37 C.F.R. §1.132 (entered by the Examiner in the Office Action mailed October 18, 2002) states:

> "The ordinary artisan did not clearly recognize the benefit of testing an individual prior to surgery and subjection to anesthesia for known genetic markers associated with conditions triggered by anesthesia or surgery at the time the invention was made." (Second Declaration of Kirk Hogan, M.D., page 2.)

The Office has never provided evidence contradicting this evidential statement of fact. Indeed, in its Decision of July 25, 2006 the Board failed to address, or even mention, this statement of fact. If the Office has evidence to the contrary it should be cited.

Moreover, in the Declaration of Dr. Douglas Baird Coursin of June 11, 2007 (entered by the Examiner in the Office Action mailed September 11, 2007) Dr. Coursin notes:

> "Prior to the perioperative genomic profiles of the present patent application, surgeons and anesthesiologists were highly motivated to detect multiple risks for complications during a surgical procedure associated with genetic variations. For example, every patient is asked whether any family members may have had complications with surgery and anesthesia, and the patient's answer is recorded on a pre-operative checklist. Nevertheless, those of ordinary skill in the art *i.e.*, anesthesiologists and surgeons, did not arrive at the solution of the presently claimed invention." (Declaration of Dr. Coursin of June 10, 2007, page 2.)

In the Final Office Action of May 21, 2008 the Office does not contest or even address these facts let alone provide contrary evidence. The Appellant notes that the proper standard is one of ordinary skill in the art, not one of exceptional skill *i.e.*, a researcher or an author of an academic manuscript. Clearly, in the Final Office Action of May 21, 2008 the Office establishes an anesthesiologist as an artisan of ordinary skill for the purposes of performing an obviousness analysis. (Final Office Action of May 21, 2008, page 9.) Even if a molecular biologist could be considered an artisan of ordinary skill, and the Appellant submits that one could not, the Office provides no evidence that such a molecular biologist would have been motivated to make the Office's combination, and thereby arrive at the claims of the present invention. For example, the Office has made no showing that a molecular biologist of ordinary skill would have been

motivated to select a perioperative course of action based on information from a genomic profile. Indeed, this is contrary to the art and the evidence in the record. Molecular biologists of ordinary skill did not and would not assemble the clinically relevant claimed markers.

To the contrary, the Appellant submits that Dr. Hogan's and Dr. Coursin's Declarations provide clear-cut, expert, and uncontested evidence that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations "for many decades", and that despite this motivation artisans of ordinary skill of any background failed to achieve the presently claimed invention at the time the invention was made.

VII.A.2. The Office Provides no Motivation to Combine Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort, and further in view of Hoon and Hacia

The non-obvious standard of §103(a) requires the Office to make a historical judgment: whether the invention would have been obvious at the time the invention was made in the past. To reach a proper non-obvious conclusion, the Office must not only step backward in time to a moment when the invention was unknown, but also avoid letting knowledge that the invention was achieved affect the Office's decision about whether it was obvious at the time it was achieved. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). The courts have recognized that meeting this standard "requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d at 999.

In an effort to preclude such an improper result, the Federal Circuit requires that the non-obvious analysis be conducted viewing the invention as a whole. *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004). Using "'hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention'" *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quoting *In re Fine*, 837 F.2d 1071, 1075 (1988), or conducting a "reference-by-reference, limitation-by-limitation analysis" fails to demonstrate how the invention is obvious in light of prior art. *Id.*, at 1074. Similarly, the Office

may not use the invention as a blueprint for linking together pieces of prior art in order to find the invention obvious. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). The Federal Circuit has referred to using the invention as a "blueprint for piecing together the prior art . . . [as] the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

The Appellant submits that the Office has clearly and improperly used hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious. The Appellant contends that, at the time the invention was made, there existed no explicit or implicit teaching or suggestion or motivation to combine elements present in the art to generate the presently claimed invention, and that the Office's speculations and conclusory statements regarding the motivation of an ordinary artisan to combine the claim elements to yield the claimed invention are in error. The Office has failed to indicate where in the references cited, or elsewhere, there is such a suggestion of desirability to combine. As the Federal Circuit has recently concluded, "knowledge of a problem and motivation to solve it **are entirely different** from motivation to combine particular references to reach the claimed method. *Innogenetics*, slip op. at 14 ("A generalized motivation to develop a method **is not** the kind of motivation required by the patent laws.")". *Innogenetics NV v. Abbott Labs.,* 512 F.3d 1363 at 1373 (Fed. Cir. 2008). (Emphasis added.) The Office must provide a basis for combining alleged art references and their elements. The Appellant asks the Office to take note of the recent Supreme Court opinion which says that a specific showing by the Office is required:

> "Often, it will be necessary … to look to interrelated teachings of multiple patents … in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR v. Teleflex*, Slip Op No. 04-1350 (April 30, 2007).

In the office Action of May 21, 2008 the Office notes:

> "The cited passage from KSR illustrates an analysis must be made specific, not that TSM is explicit. The analysis of KSR allows for a person with ordinary skill to have a good reason to pursue known options within his or her technical grasp." (Final Office Action of May 21, 2008, page 23.)

The Appellant notes that the Office's rejection has been neither specific, nor has the Office provided evidence that the claims of the present application were within the technical grasp of the anesthesiologist or perioperative caregiver of ordinary skill at the time the invention was made.

To the contrary, in the Declaration of Dr. Douglas Baird Coursin of June 10, 2007 Dr. Coursin explains that there was no suggestion or teaching in the prior art or elsewhere for the perioperative genomic profiles of the presently claimed invention. Dr. Coursin notes:

> "The perioperative genomic profiles of the present patent application represent a completely novel approach that is not obvious in view of existing technologies. To my knowledge, no one previously proposed or disclosed perioperative genomic profiles that would be successful in screening a patient perioperatively to determine a risk for multiple complications during a surgical procedure." (Declaration of Dr. Coursin of June 10, 2007, page 2.)

In a situation like the present one, there may be no better evidence of non-obviousness than the failure of an entire field to solve their primary problem, even with a wealth of information and technology known in the literature. In the Final Office Action of May 21, 2008 the Office does not contest or even address these facts in direct refutation of the Office's speculations. The field failed to realize the solution because the solution was not obvious to these skilled artisans. These skilled artisans would not, and did not, see the combinations the Office proposes that they should have and would have seen.

In the Final Office Action of May 21, 2008 the Office notes:

> "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia." (Final Office Action of May 21, 2008, page 9.)

The Appellant notes that the "the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed" stand in stark contrast to the absence of anyone having come up with the invention prior to the filing of the present application. The Appellant notes that most of the references predate the filing of the application by many years. In view of all of this knowledge in the art, no one had come up with the invention. The Office has not found a single anticipatory reference. Why is this?

Dr. Coursin's declaration provides an explanation. Dr. Coursin is one of the leading anesthesiologists in the country, and has been for many years. Dr. Coursin explains that skilled artisans, such as anesthesiologists, have as a primary mission to solve the problem solved by the present invention. Yet even with this long-felt need and years of searching by innumerable practitioners, no one solved this long-felt need using the approach of the present invention:

> ""However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made." (Declaration of Dr. Coursin of June 10, 2007, page 3.)

In the Final Office Action of May 21, 2008 the Office notes:

> "The declaration under 37 CFR 1.132 filed on June 14, 2007 is insufficient to overcome the rejection as set forth in the last Office action because: it states that the claimed subject matter solved a problem that was long standing in the art. However, there is no

showing that other so ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would solve the problem. See MPEP 716.04. Here, the declaration of Dr. Coursin fails to provide evidence in the opinion declaration that the ordinary skilled artisans were working on the problem and for how long. Moreover, the declaration fails to provide any evidence that those working in the art on the problem knew of Quane, Miller, Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans et al, Hoon et al, or Hacia references and were still unable to solve the problem. Thus, the declaration is insufficient to overcome the 103 rejection of record." (Office Action of May 21, 2008, page 24.) (Emphasis in original.)

To the contrary, the Appellant submits that Dr. Coursin's Declaration provides clear-cut, expert, and uncontested evidence that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before". (Emphasis added.) Dr. Coursin's Declaration provides evidence that the need was persistent and recognized by those of ordinary skill in the art:

"I have been in the practice of Anesthesiology and Critical Care Medicine for 26 years. During this entire time, and well before, the overriding mission of anesthesiologists, surgeons and other caregivers in the perioperative period has been to reduce the risk of adverse outcomes to the minimum for each patient. As well, it has long been recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery. Despite this heightened level of vigilance, and intense focus on a shared mission, no one taught or suggested perioperative genomic profiles before the present patent application." (Declaration of Dr. Coursin of June 10, 2007, page2.)

These facts were pointed out to the Office in the Response to Office Action of September 11, 2007. In the Office Action of May 21, 2008 the Office fails to rebut or even to address this evidence in direct refutation of the Office's speculations.

The Appellant submits that the Office's rejection is based on hindsight knowledge of the invention wherein the Office has assumed what skilled artisans *should have* thought of the invention in view of numerous disparate pieces of prior art. In making the rejection, the Office (*i.e.*, not one of skill in the art, and who is in possession of hindsight knowledge of the invention), has *seen* an invention that the entire world of skilled artisans, focused for many years on the exact problem solved by the invention, had failed to see. Artisans, of ordinary and extraordinary skill in the field, who have devoted their careers to solving this problem, failed to put together the Office's combination of references, and failed to solve the problem. The only logical explanation is that the invention is non-obvious. In the Final Office Action of May 21, 2008 the Office does not contest or even address these facts.

Notably missing from the Office's rejection is placement in the hands and minds of the appropriate skilled artisans of: 1) the prior art of record (is this the type of work one skilled in the art would have reviewed in assessing the problem?); and 2) the mental and experimental process for modifying the art to arrive at the invention (even if they would have reviewed the cited art, would they have put the pieces together and modified the pieces appropriately?). At no point in the Final Office Action of May 21, 2008 does the Office provide evidence of the handling of the references in the hands and minds of the appropriate skilled artisan. Regardless, even if the Office had done this, the evidence of long-felt but unresolved need demonstrates that skilled artisan did not, and would not, arrive at the invention. If it were obvious, they would have done it years before the filing of the present application. In the Final Office Action of May 21, 2008 the Office does not contest or even address these facts.

The Supreme Court specifically states:

> "Often it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made

explicit." (*KSR Int'l Co. v. Teleflex, In.,* 550 U.S., 127 S. Ct. 1727 (2007).) (Emphasis added.)

The Appellant asserts that in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of 9 alleged prior art elements (*vs.* 2 prior art references in *KSR v. Teleflex*), the Office has clearly failed to identify the reason why a person of ordinary skill in the art would have made the combination in the manner claimed. In making such a reconstruction, the Office may only take into account the common knowledge which was within the level of ordinary skill at the time the claimed invention was made, and may not include, as here, knowledge gleaned only from the Appellant's disclosure or unsupported assumptions about the mindset of the skilled artisan. (See *In re McLaughlin*, 443 F/2d 1392, 170 USPQ 209 CCPA, 1971.) The determination of whether a combination is a predictable variation of the prior art must be evaluated from the perspective of the person of ordinary skill in the art at the time claimed invention was made. Dr. Hogan's and Dr. Coursin's Declarations provide material evidence that Office's speculations regarding the level of ordinary skill are in clear error.

The Appellant notes that at the time the invention was made skilled artisans would not have looked, and did not look, to the Office's non-analogous literature. Moreover, even had they, the Office has never provided evidence that the skilled artisan would have known what to do with the non-analogous art to arrive at the various inventions now claimed. For example, the Office has never provided a reason why such a skilled artisan would have culled the Office's sub-set of references out of the thousands of references in the molecular biology art, let alone read them, understand them, and combine them in the specific manner proposed by the rejections.

In the Final Office Action of May 21, 2008 the Office notes:

"As provided in MPEP 716.02(a) evidence must show unexpected results. The opinion declaration of Dr. Coursin does not appear to show any unexpected results." (Final Office Action of May 21 2008, page 24.)

To the contrary, in the Declaration of June 10, 2007, Dr. Coursin explains that he himself has since used embodiments of the invention and achieved excellent, and unexpected, results:

"In turn, a mean of 11 mutant alleles in aggregate (*i.e.*, homozygous plus heterozygous mutant polymorphisms) per patient were observed at loci comprising the perioperative genomic panel. These unexpected results demonstrate that significant genetic heterogeneity is present in most patients in advance of surgery that is not accounted for using contemporary tools for detection, *e.g.*, a family history check-box." (Declaration of Dr. Coursin of June 10, 2007, page 3.)

MPEP 716.02 states:

"Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected." (MPEP 716.02)

In the Response to Office Action of September 11, 2007 the Appellant reminded the Office that the standard for the presence or absence of motivation, long-felt need, and unexpected results does not apply to the expectations of the Office in possession of the Application, but rather to the expectations of the ordinary artisan (*i.e.*, anesthesiologists and perioperative caregivers) at the time the invention was made. Clearly, Dr. Coursin's declaration provides evidence that the claims of the present application not only meet, but exceed these tests. In the Office Action of May 21, 2008 the Office fails to rebut or even to address this evidence in direct refutation of the Office's speculations.

Moreover, Dr. Coursin's declaration is not an "opinion declaration" as characterized by the Office (Final Office Action of May 21, 2008, page 24.), nor has the Office provided an interpretation of what the Office believes is the definition of an "opinion declaration". Contrary to the Office's characterization, Dr. Coursin's declaration provides objective evidence of record that the Office has failed to rebut or even address in the Response to Office Action of September 11, 2007. For example, Dr. Coursin's declaration factually describes the state of the art and the knowledge, capabilities, and actions of skilled artisans in the relevant time period.

In the Final Office Action of May 21, 2008 the Office notes:

"Moreover it is completely not unexpected that detecting these genetic mutations can avoid deleterious outcomes and save lives." (Final Office Action of May 21, 2008, page 25)

In relying upon these arguments to support a prima facie case of obviousness, the Office has made a number of errors. First, The Office's acknowledgment of the benefits of the claimed invention made after the Office was in possession of the specification and claims does not, and cannot, substitute for substantial evidence of what an artisan of ordinary skill would or would not have been motivated to do at the time the invention was made. To the contrary, the in the Final Office Action of May 21, 2008 the Office improperly persists in asserting new standards of the ordinary artisan's motivation to combine references *i.e.*, to "avoid deleterious outcomes", and to "save lives." In *In re Sang Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Office. *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002). On multiple occasions in the prosecution of the present application the Office has had the opportunity to address this holding, and has never done so.

The Appellant submits that the Office's improper combination of references, and failure to respond to numerous facts in the Appellant's Response to the Office Action of September 11, 2007 preclude a finding of prima facie obviousness of the claims.

VII.A.3. Missing Elements in Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort, and further in view of Hoon and Hacia

The Appellant submits that the Office's combination of references fails to disclose not just one, but multiple elements of the claimed invention. Thus, the Office's references fail to establish *prima facie* obviousness of the claims.

In the Final Office Action of May 21, 2008 the Office concedes that Miller does not specifically teach analyzing blood prior to surgery for "two or more known genetic markers associated with two or more conditions." (Final Office Action of May 21, 2008, page 2.) The Appellant notes that none of the Office's additional 8 references alone or in combination remedy

the defects of these elements missing from Miller, nor has the Office indicated where these missing elements are to be found in the Office's combinations.

II.A.3.a. The Office's combination of references is missing the elements of selecting a perioperative course of action based on information from a perioperative genomic profile, and performing a surgical procedure (Claim 106)

In the Final Office Action of September May 21, 2008 the Office argues:

"The response asserts Claim 106 requires selecting a perioperative course of action based upon information from the genomic profile. The examiner fully agrees with this assertion. However, given the cited combination of references, once the ordinary artisan realized a patient was predisposed to have an adverse reaction to anesthesia or other condition, the ordinary artisan would have selected a course of action consistent with this discovery and acted appropriately." (Final Office Action of May 21, 2008, page 12.)

And:

"Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from the genetic profile and used the information in a prudent manner to avoid any complications that may exist given information generated from the genetic analysis." (Final Office Action of May 21, 2008, page 12.) (Emphasis added.)

The Appellant respectfully disagrees.

First, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever other than the Office's notions in hindsight while in possession of the application. In the Final Office Action of May 21, 2008 the Office fails to provide substantial evidence of the missing elements at the time the invention was made.

Second, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do in view of the Office's interpretation of the KSR opinion. This analysis does not legally compensate for a need to show the missing elements in the evidence provided with the rejection. In the Final Office Action of May 21, 2008 the Office fails to indicate where the KSR opinion grants permission to the Office to "read-in" one or more missing elements to the claims.

Third, the Office's speculations concerning the professional liabilities of a surgeon, anesthesiologist or nurse clearly do not provide the missing elements, or remedy the rejection's missing elements. For example, the claims do not recite the element of "professional liability."

The Appellant notes that the element "selecting a perioperative course of action based on information from said genomic profile" is a method step that limits the scope of claim 106. Claim 106 is thereby limited to a process that includes selecting a perioperative course of action based on the results of the perioperative genomic profile. In the Final Office Action of May 21, 2008 the Office has failed to point out where in the Office's 9 cited references this element ("selecting a perioperative course of action") based on information from a perioperative genomic profile is to be found. Only by knowing the specific results of the perioperative genomic profile in a specific patient is it possible to select a specific perioperative course of action on the basis of the specific results. None of the office's references, alone or in combination, provide these elements.

As well, the element "performing said surgical procedure wherein said perioperative course of action is used by at least one of the group consisting of an anesthesiologist, a nurse, and a surgeon" is a method step that limits the scope of claim 106. Claim 106 is thereby limited to a process that includes performing a surgical procedure based on the results of the perioperative genomic profile. The Office's cited references provide no guidance regarding which two or more nucleic acid markers in two or more genes associated with two or more conditions may be used to carry out a surgical procedure correctly. The only reference cited by the Office in response to the fact of these missing elements is Quane. (Final Office Action of May 21, 2008, pages 13-14). However, Quane teaches only a single condition arising from alleles in only a single gene. Nor do the Office's cited references provide guidance to the anesthesiologist, nurse, or surgeon to balance information from the components of the

perioperative genomic profile. In the Final Office Action of May 21, 2008 the Office has failed to indicate where in the Office's combination of references these elements are to be found, or to respond to these facts presented in the Appellant's Response to Office Action of September 11, 2007.

II.A.3.b. The Office's combination of references is missing the element of a perioperative course of action based on information from a perioperative genomic profile for a first surgical procedure (Claim 107)

In the Final Office Action of May 21, 2008 the Office notes:

> "The response argues that the combination or references is missing the limitation that a perioperative course of action is for the first surgical procedure. (claim 107). This argument has been reviewed but is not persuasive. The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent complications. The response asserts that Quane reference (sic) merely suggests testing after a patient has had a prior complication during a surgical procedure. This argument has been reviewed but is deemed not persuasive because it would be common sense to test for a mutation known to be negatively associated with a surgical procedure prior to surgery to prevent complications as previously stated. (Final Office Action of May 21, 2008, page 14.) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculations of what an ordinary artisan would or would not have been motivated to do. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office has failed to respond to this deficiency.

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 107. The element of a perioperative course of

action based on information from a perioperative genomic profile for a first surgical procedure does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office's citation of the Quane reference merely suggests testing for a single disorder in a single gene after a patient has had a prior complication during a surgical procedure. The Office has not indicated where the element of selecting a perioperative course of action based on information from a genomic profile "for a first surgical procedure" is to be located in the Office's cited references. Thus, the Office's references fail to establish *prima facie* obviousness of the claims.

II.A.3.c. The Office's combination of references is missing the element of a course of action based on information from a perioperative genomic profile for administration of anesthesia during a medical procedure (Claims 117, 168)

In the Final Office Action of May 21, 2008 the Office notes:

> "The response argues that the combination of references is missing the limitation that the course of action comprises administration of anesthesia during a medical procedure. This argument has been reviewed but is not persuasive. The Quane reference teaches that "once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." (Office Action of May 21, 2008, page 15.)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claims 117 and 168. The element of a course of action based on information from a perioperative genomic profile for administration of anesthesia during a medical procedure does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office's citation of the Quane reference merely suggests testing for a single disorder in a single gene. Quane does not teach or suggest the element of a course of action based on information from a perioperative genomic profile.

In the Final Office Action of May 21, 2008 the Office notes:

"The response attacks Quane individually, but fails to consider the combination of references for teachings (sic) perioperative genomic profile for administration of anesthesia during a medical procedure." (Final Office Action of May 21, 2008).

The Appellant respectfully disagrees and notes that in this assertion the Office has made a number of errors. First, as noted in the Response to Office Action of September 11, 2007 the Appellant has considered the Office's combination of references and asserts they are wanting: "The Examiner has not indicated where this element is to be located in the Examiner's cited references." (Response to Office Action of September 11, 2007, page 24.) Second, the Quane reference is the only reference discussed by the Office. Third, the deficiencies of the Quane reference in lacking "the element of a course of action based on information from a perioperative genomic profile for administration of anesthesia during a medical procedure" are not cured by the remainder of the Office's references. Nor has the Office indicated where in the Office's combination of references the missing elements are to be found.

II.A.3.d. The Office's combination of references is missing the element of a perioperative genomic profile comprising a presymptomatic risk (Claim 120)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 120. The element of a perioperative genomic profile comprising a presymptomatic risk does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Office Action of May 28. 2001 the Office notes:

"The response argues that the combination of references is missing the limitation that the genomic profile comprises information comprising presympotomatic risk. This argument has been reviewed but is not persuasive. The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test

for MH prior to triggering a response that would cause death." (Final Office Action of May 21, 2008, page 16.) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing element in the Office's combination of references with an argument based on the Office's speculations of what an ordinary artisan would or would not have been motivated to do.

The Office's response in the Final Office Action of May 21, 2008 when confronted with these facts in the Response to Office Action of September 11, 2207 notes:

"The ordinary artisan would be motivated to test for MH prior to triggering a response that would cause death. The response filed March 11, 2008 disagrees with the analysis of the state of the art and what the skilled artisan would be motivated to have done. However, for reasons of record, the rejection is maintained." (Final Office Action of May 21, 2008, pages 15-16). (Emphasis added.)

Accordingly, the Appellant notes that the Office has failed to supply the missing element of a perioperative genomic profile comprising a presymptomatic risk with evidence sufficient to meet the Office's burden. In particular, the Office has failed to address the relevance of Quane and MH to claims 143, 160 and 186.

II.A.3.e. The Office's combination of references is missing the element of a perioperative genomic profile comprising information for differential diagnosis of co-existing diseases (Claim 121)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 121. The element of a perioperative genomic profile comprising information for differential diagnosis of co-existing diseases does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

"The ordinary artisan would be motivated to diagnose the specific condition that is associated with poor response to anesthesia. The analysis of the MH gene would allow for differential diagnosis between MH and other anesthesia triggering conditions." (Final Office Action of May 21, 2008, pafge 16.) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculations of what an ordinary artisan would or would not have been motivated to do. Accordingly, the Appellant notes that the Office has failed to supply the missing element of a perioperative genomic profile comprising information for differential diagnosis of co-existing diseases with evidence sufficient to meet the Office's burden. In particular, the Office has failed to address the relevance of Quane and MH to claims 143, 160 and 186.

II.A.3.f. The Office's combination of references is missing the element of selecting a surgical procedure treatment course of action (Claim 127)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 127, or of claims that are dependent thereupon. The element of selecting a surgical procedure treatment course of action does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

"Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from the genetic profile and used the information in a prudent manner to avoid any complications

that may exist give the information generated from the genetic analysis." (Final Office Action of May 21, 2008, page 17.) (Emphasis added.)

The Appellant respectfully disagrees. First, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Second, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculations of what an ordinary artisan would or would not have been motivated to do. Third, the Office's speculations concerning professional liability do not provide the missing elements, or remedy the rejection's defects. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.g. The Office's combination of references is missing the element of non-invasive surgery (Claims 139, 179)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claims 139 and 179. The element of non-invasive surgery does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

"The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test for MH prior to triggering a response that would cause death." (Office Action of May 21, 2008, pages 17-18.) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing

elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do. For example, none of the Office's references alone or in combination teach or suggest the element of non-invasive surgery. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record. In particular, the Office has failed to address the relevance of Quane and MH to claims 143, 160 and 186.

II.A.3.h. The Office's combination of references is missing the element of selection of monitoring procedures based on the results of a perioperative genomic profile (Claim 148, 175)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claims 148 and 175. The element of selection of monitoring procedures based on the results of a perioperative genomic profile does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

> "The response asserts that the combination of elements fails to teach selection of monitoring procedures based upon the profile. This argument has been reviewed but deemed not persuasive. The ordinary artisan would have been motivated to have monitored procedures." (Final Office Action of May 21, 2008, page 18.) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an

ordinary artisan would or would not have been motivated to do. For example, none to the Office's references teach or suggest selection of monitoring for thromboembolism, or any trait or phenotype, based on the results of a perioperative genomic profile. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.i. The Office's combination of references is missing the element of obtaining consent from a perioperative subject to assay a sample for genetic variations (Claim 149)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 149, or of claims that are dependent thereupon. The element of obtaining consent from a perioperative subject to assay a sample for genetic variations does not appear in Miller. The Office has not indicated where this element is to be located in the Miller, or in any of the other of the Office's references alone or in combination.

In the Final Office Action of May 21, 2008 the Office notes:

> "The response asserts that the combination of references is missing the element of obtaining consent from a perioperative subject to assay a sample for genetic variation (claim 149). Despite Miller teaching obtaining consent for perioperative tests and analysis, the response asserts that this is not consent for a genetic variation test. This argument has been reviewed but is not persuasive. The ordinary artisan would have been motivated to have obtained consent for ANY procedure in the medical field, as is routine and customary in the field to avoid malpractice allegations." (Final Office Action of May 21, 2008, pages 18-19.) (Underlining added.)

The Appellant respectfully disagrees. First, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Second, the Office improperly responds to the fact of missing elements in the Offices' combination of references with an argument based on the Office's speculation of what an ordinary artisan would

or would not have been motivated to do by, for example, fear of "malpractice allegations". Third, the Office's speculations concerning professional liability do not provide the missing elements, or remedy the rejection's defects. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.j. The Office's combination of references is missing the element of distributing the results of a patient's perioperative genomic profile according to the patient's preference wherein the distributing is selected from the group consisting of destroying the results, saving the results for future access by the patient, saving the results for future access by a clinician, and donating the results for research (Claims 149, 189)

The Appellant notes that the element of "distributing said results of said patient's said genomic profile according to said patient's preference wherein said distributing is selected from the group consisting of destroying said results, saving said results for future access by said patient, saving said results for future access by said clinician, and donating said results for research;" does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where in the Office's cited references the element "distributing said results of said patient's said genomic profile according to said patient's preference" is to be located.

In the Final Office Action of May 21, 2008 the Office notes:

> "It is not apparent what other choices were available to the patient. Thus, the ordinary artisan would have been motivated to have done one of these two actions." (Office Action of September 11, 2007, page 17.) (Emphasis added.)

The Appellant respectfully disagrees. First, the missing element is drawn to the patient's preference or choice, not to the Office's speculations regarding the ordinary artisan's motivation in either destroying or saving results. In the Final Office Action of May 21, 2008 the Office fails to indicate where in the Office's combination of references this choice is offered to a patient.

Second, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.k. The Office's combination of references is missing the element of distributing the patient's sample according to the patient's preference wherein the distributing is selected from the group consisting of destroying the sample, saving the sample for future access, and donating the sample for research (Claims 149, 189)

The Appellant notes that the element of "distributing said patient's said sample according to said patient's preference wherein said distributing is selected from the group consisting of destroying said sample, saving said sample for future access, and donating said sample for research." does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where in the Office's cited references "distributing said patient's said sample according to said patient's preference" is to be located.

In the Final Office Action of May 21, 2008 the Office notes:

> "The ordinary artisan would have either destroying the sample or saving the sample (sic). It is not apparent what other choices were available to the patient. Thus the ordinary artisan would have been motivated to have done one of these two actions." (Final Office Action of May 21, 2008, page 20.)

The Appellant respectfully disagrees. First, the missing element is drawn to the patient's preference or choice, not to the Office's speculations regarding the ordinary artisan's motivation in either destroying or saving the sample. In the Final Office Action of May 21, 2008 the Office fails to indicate where in the Office's combination of references this choice is offered to a

patient. Second, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.l. The Office's combination of references is missing the element of a computer program comprising instructions which direct a processor to analyze results of a perioperative genomic profile (Claim 150)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 150. The element of a computer program comprising instructions which direct a processor to analyze results of a perioperative genomic profile does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

> "The response asserts that the combination of references is missing the element of a computer program comprising instructions which direct a processor to analyze results of a perioperative genomic profile. This argument has been reviewed but is not persuasive. Hacia teaches mutations are detected by a minisequencing assay using an algorithm." (Final Office Action of May 21, 2008, page 20.)

The Appellant notes that Hacia fails to remedy the defects of the Office's rejection. For example, Hacia does not teach or suggest a perioperative genomic profile. As well, Hacia does not teach or suggest a processor to analyze results of a perioperative genomic profile. Moreover, Hacia does not teach or suggest a computer program comprising instructions which direct a processor to analyze results of a perioperative genomic profile. In the Final Office Action of

May 21, 2008 the Office has not indicated where these elements that are missing in the Office's combination of references are to be found in Hacia, or in any of the other references cited by the Office alone or in combination. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.m. The Office's combination of references is missing the element of thrombosis associated with variant alleles of *MTR, MTRR,* and *CBS* (Claims 173, 174)

The Appellant notes that none of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding methionine synthase (*MTR*). As well, none of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding methionine synthase reductase (*MTRR*). Morevoer, none of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding cystathionine beta-synthase (*CBS*).

II.A.3.n. The Office's combination of references is missing the element of providing a kit comprising a computer program on a computer readable medium comprising instructions which direct a processor to analyze data derived from use of reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, the subject being a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNFα* so as to generate a genomic profile for use in selecting a perioperative course of action for the subject (Claim 186)

In the Final Office Action of May 21, 2008 the Office notes:

"The response asserts that the combination of references is missing the element of a kit comprising a computer program." (Office Action of May 21, 2008, page 21.)

The Appellant notes that the Office has misread claim 186. Contrary to the Appellant's characterization, claim 186 recites a kit comprising a computer program on a computer readable medium comprising instructions which direct a processor to analyze data derived from use of reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, the subject being a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNF*α so as to generate a genomic profile for use in selecting a perioperative course of action for the subject.

The Appellant notes that Hacia does not teach or suggest such a computer program on a computer readable medium, nor does such a computer program on a computer readable medium appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, or Hoon alone or in combination. In the Final Office Action of May 21, 2008 the Office has not indicated where this element is to be located in the Office's cited references. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office notes:

"The response filed March 11, 2008 disagrees with the analysis of the art and what the skilled artisan would be motivated to have done. However, for the reasons of record, the rejection is maintained." (Final Office Action of May 21, 2008, pages 21-22.) (Emphasis added.)

The Appellant respectfully disagrees. First, the Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of

references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.o. The Office's combination of references is missing the element of generating a perioperative genomic profile with the kit of Claim 186 (Claim 186)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 186. The element of generating a perioperative genomic profile with the kit of Claim 186 does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

> "The response asserts that the combination of references is missing the element of teaching of a kit for generating a perioperative genomic profile. . . . The providing of the computer and algorithm meets the requirement of a kit. A kit, without more, is merely a composition of reagents." (Final Office Action of May 21, 2008, page 22.)

The Appellant notes that the Office has misread claim 186. Claim 186 is a claim dependent upon the independent method claim 149. The element "generating said genomic profile with said kit" is a step that limits the scope of claim 149 in that it dictates the parameters of the encoded software provided in the kit. The Appellant notes that Hacia does not teach or suggest this limitation, nor does this limitation appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, or Hoon alone or in combination. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.p. The Office's combination of references is missing the element of selecting perioperative genomic profile markers by the criteria of analytical validity, clinical validity and clinical utility (Claim 189)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claims 189, and claims that are dependent thereupon. The element of selecting perioperative genomic profile markers by the criteria of analytical validity, clinical validity and clinical utility does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

In the Final Office Action of May 21, 2008 the Office notes:

> "The ordinary artisan would have selected those markers, as discussed above, based upon these three criteria. Analyzing markers which have no utility or validity would not have been motivated by the art." (Final Office Action of May 21, 2008, pages 22-23) (Emphasis added.)

The Appellant respectfully disagrees. The Office's observations regarding missing elements in the claims are conclusory and unsupported by any evidence whatsoever. Moreover, the Office improperly responds to the fact of missing elements in the Office's combination of references with an argument based on the Office's speculation of what an ordinary artisan would or would not have been motivated to do. These facts were brought to the Office's attention in the Response to Office Action of September 11, 2007. In the Final Office Action of May 21, 2008 the Office fails to respond, address or even consider these clear cut facts of record.

II.A.3.q. The Office's combination of references is missing the element of genetic markers consisting of unique genomic identifiers (Claim 191)

The Appellant respectfully notes that the Office's references both individually, and in combination, fail to teach all elements of claim 191. The element of unique genomic identifiers does not appear in Miller, Quane, Acta, La Du, Pharmacogenetics, Evans, Poort, Hoon or Hacia. The Office has not indicated where this element is to be located in the Office's cited references.

VII.A.4. The Office has erred in not properly determining the scope and contents ofthe prior art, and in ascertaining differences between the prior art and the presently claimed invention

In the Final Office Action of May 21, 2008 the Office concedes:

> "Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".
>
> However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH)". (Final Office Action of May 21, 2008, page 2.)

The Appellant notes that the Office has failed to establish a prima facie case of obviousness because the Office has erred in determining the scope and contents of the alleged prior art, and in ascertaining differences between the alleged prior art and the claims at issue. For example, contrary to the Office's characterization, claims 160 and 186 do not recite variant alleles in *RYR1*. Moreover, claim 143 does not recite malignant hyperthermia. In the Final Office Action of May 21, 2008 the Office does not express the relevance of the Quane reference to claim 143, 160, and 186.

Moreover, the Office notes:

> "Specifically, codeine should be administered with care to individuals having certain BchE mutations." (Final Office Action of May 21, 2008, page 9.)

To the contrary, the Appellant notes that codeine is metabolized by CYP2D6 not BChE. Thus, the rejection is based on factually incorrect assumptions.

VII.A.5. Claims 143 - 148 Are Not Obvious and Have Not Been Examined

In the Final Office Action of May 21, 2008 the Office has rejected claims 143-148. However, in the Final Office Action of May 21, 2008 the Office has not examined independent claims 143 or 144, or claims dependent thereupon. Nowhere in the rejections are the elements of these claims addressed. Moreover, because Quane does not teach or suggest the genetic markers or conditions of claim 143, or the first marker in a first gene and a second marker in a second gene of claim 144, the Office has not, and cannot, point to Quane as a reference providing motivation to combine the elements of claims 143-148.

VII.A.6. Conclusion

In view of the points of non-obviousness discussed above, it is clear claims 106–124, 127-133, 135-150, 161-186, 189 and 191 are not obvious over the Office's combination of Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia.

VII. B. Ground of Rejection 2 – Whether claims 151-160, 187-188, and 190 are obvious over Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia and further in view of Lapointe.

In the Final Office Action of May 21, 2008 the Office notes:

> "Therefore, it would have been prima facie obvious at the time the invention was made to have designed a neural network as taught by Lapointe for the perioperative screening method of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia (Final Office Action of May 21, 2008, page 27.)

The Appellant respectfully disagrees. Claims 151-160, and 187-188 depend upon claim 149 and are non-obvious for at least the same reasons that claim 149 is non-obvious. As well,

claim 190 depends upon claim 189 and is non-obvious for at least the same reasons claim 189 is non-obvious.

Moreover, the Appellant submits that the Office's combination of references fails to disclose not just one, but multiple elements of the claimed invention. For example, the Office's combination of references fails to teach or suggest privacy, privacy security, or the privacy protocols of claims 187 and 188. Nor does the Office's combination of references teach or suggest elements of an integrated electronic system for organization of selection of two or more genetic markers, subjecting a sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions, and distributing the results of a patient's perioperative genomic profile according to the patient's preference of Claim 190. As well, the Appellant submits that there is no motivation to combine the cited references in the manner suggested by the Final Office Action of May 21, 2008. For example, Lapointe does not teach or suggest characterization of DNA, nucleic acids, genetic testing, perioperative care, or provide any teaching or suggestion to make the Office's combination of references. In the Final Office Action of May 21, 2008 the Office fails to indicate why an artisan of ordinary skill would turn to Lapointe for guidance. In addition, the Appellant submits that even if combined, there would be no expectation of success.

VII.C. Ground of Rejection 3 – Whether claim185 is obvious over Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia and further in view of Lyamichev.

In the Final Office Action of May 21, 2008 the Office notes:

> "Therefore, it would have been prima facie obvious at the time the invention was made to have modified the detection methods of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia to encompass invader directed analysis as taught by Lyamichev." (Final Office Action of May 28, 2008, page 29.)

The Appellant respectfully disagrees. Claim 185 depends upon claim 149, and is non-obvious for at least the same reasons that claim 149 is non-obvious.

Moreover, the Appellant submits that there is no motivation to combine the cited references in the manner suggested by the Final Office Action of May 21, 2008. As well, the Appellant submits that even if combined, there would be no expectation of success.

VII.D. Ground of Rejection 4 – Whether claims 125 and 134 are obvious over Miller in view of Quane or Acta and La Du or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia and further in view of the specification (Tables 1-4).

In the Final Office Action of May 21, 2008 the Office notes:

> "Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the high throughput analysis of operative complications that were known at the time of the invention." (Final Office Action of May 21, 2008, page 30.)

The Appellant respectfully disagrees. Claim 125 depends upon claim 106 and is non-obvious for at least the same reasons that claim 106 is non-obvious. Similarly, claim 134 depends upon claim 127 and is non-obvious for at least the same reasons that claim 127 is non-obvious.

Moreover, the Appellant submits that the Office's combination of references fails to disclose not just one, but multiple elements of the claimed invention. For example, the Office's combination of references fails to teach or suggest the closed panel of alleles in genes encoding BChE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, and CPT2, and TNFα of claims 125 and 134. The references cited by the office provide alleles in one, or at most, two genes encoding the claimed proteins, but not this specific combination of 11 proteins and no other. Nor has the Office provided evidence or reasoning why this specific combination as a claim element is obvious in view of "any number of genes" to which the Final Office Action of May 21, 2008 refers. The Appellant asserts that there is nothing in the Office's combination of references or elsewhere in the prior art that teaches or suggests this combination of alleles as a limitation.

As well, none of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene

encoding methionine synthase (*MTR*). None of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding methionine synthase reductase (*MTRR*). None of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding cystathionine beta-synthase (*CBS*). None of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding carnitine palmitoyl transferase II (*CPT2*).

Moreover, the Appellant submits that there is no motivation to combine the cited references in the manner suggested by the Office Action of May 21, 2008. As well, the Appellant submits that even if combined, there would be no expectation of success.

VIII. CLAIMS APPENDIX

1. – 105. (cancelled)

106. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile;

c) selecting a perioperative course of action based on information from said genomic profile, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure; and

d) performing said surgical procedure wherein said perioperative course of action is used by at least one of the group consisting of an anesthesiologist, a nurse, and a surgeon.

107. (previously presented) The method of Claim 106, wherein said surgical procedure is the first surgical procedure for said subject.

108. (previously presented) The method of Claim 106, wherein previous said surgical procedures on said patient have been with one or more complications.

109. (previously presented) The method of Claim 106, wherein said course of action comprises administration of anesthesia during a surgical procedure.

110. (previously presented) The method of Claim 109, wherein said anesthesia is

general anesthesia.

111. (previously presented) The method of Claim 110, wherein said general anesthesia is inhalational anesthesia.

112. (previously presented) The method of Claim 110, wherein said general anesthesia is intravenous anesthesia.

113. (previously presented) The method of Claim 109, wherein said anesthesia is regional anesthesia.

114. (previously presented) The method of Claim 113, wherein said regional anesthesia is spinal or epidural anesthesia.

115. (previously presented) The method of Claim 106, wherein said surgical procedure is non-invasive surgery.

116. (previously presented) The method of Claim 106, wherein said surgical procedure is invasive surgery.

117. (previously presented) The method of Claim 106, wherein said course of action comprises administration of anesthesia during a medical procedure.

118. (previously presented) The method of Claim 106, wherein said genomic profile comprises information pertaining to a pharmacodynamic risk.

119. (previously presented) The method of Claim 106, wherein said genomic profile comprises information pertaining to a pharmacokinetic risk.

120. (previously presented) The method of Claim 106, wherein said genomic profile comprises a presymptomatic diagnosis.

121. (previously presented) The method of Claim 106, wherein said genomic profile comprises information pertaining to differential diagnosis of co-existing diseases.

122. (previously presented) The method of Claim 106, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes, said genes selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2, F5*, *RYR1*, *CACNA1S*, and *CPT2*.

123. (previously presented) The method of Claim 122, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes.

124. (previously presented) The method of Claim 122, wherein said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes.

125. (previously presented) The method of Claim 106, wherein said genomic profile consists of alleles in genes encoding BChE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, and CPT2, and TNFα.

126. (cancelled)

127. (previously presented) A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile;

c) selecting a surgical procedure treatment course of action based on information from said genomic profile; and

d) subjecting said subject to a surgical procedure.

128. (previously presented) The method of Claim 127, wherein said genetic markers are associated with a pharmacological response.

129. (previously presented) The method of Claim 128, wherein said pharmacological response is to an anesthetic.

130. (previously presented) The method of Claim 128, wherein said pharmacological response is to drugs used in anesthetic practice.

131. (previously presented) The method of Claim 127, wherein said two or more nucleic acid genetic markers comprises a mutation in two or more genes associated with two or more conditions, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2.*

132. (previously presented) The method of claim 131, wherein said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

133. (previously presented) The method of claim 131, wherein said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

134. (previously presented) The method of Claim 127, wherein said genomic profile consists of alleles in genes encoding BChE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, and CPT2, and TNFα.

135. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting genetic markers in genes clinically associated with conditions consisting of butyrylcholinesterase deficiency, impaired debrisoquine metabolism, sepsis, thrombosis, and malignant hyperthermia to generate a genomic profile;

c) directing a physician to a perioperative treatment course of action based on information from said genomic profile for determining a risk for complications during a surgical procedure; and

d) subjecting said subject to a surgical procedure.

136. (previously presented) The method of Claim 135, wherein said physician is an anesthesiologist.

137. (previously presented) The method of Claim 135, wherein said course of action comprises administration of anesthesia during a surgical procedure.

138. (previously presented) The method of Claim 135, wherein said physician is a surgeon.

139. (previously presented) The method of Claim 135, wherein said surgical procedure is non-invasive surgery.

140. (previously presented) The method of Claim 135, wherein said surgical procedure is invasive surgery.

141. (previously presented) The method of Claim 135, wherein the said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

142. (previously presented) The method of Claim 135, wherein the said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

143. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency and impaired debrisoquine metabolism to generate a genomic profile:

c) directing a physician to a perioperative treatment course of action based on information from said genomic profile for determining a risk for complications during a surgical procedure; and

d) subjecting said subject to a surgical procedure.

144. (previously presented) A method for selecting an appropriate anesthesia treatment during surgery, comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;

b) subjecting said sample to an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said markers are known to be associated with adverse responses to anesthesia treatment; and

c) subjecting said subject to a surgical procedure, wherein said assay results are consulted by a physician in selecting an appropriate anesthesia treatment for said subject based on information from said assay results.

145. (previously presented) The method of Claim 144, wherein said physician is an anesthesiologist.

146. (previously presented) The method of Claim 144, wherein said selecting comprises selection of dosages of anesthesia.

147. (previously presented) The method of Claim 144, wherein said selecting comprises selection of anesthesia compounds.

148. (previously presented) The method of Claim 144, wherein said selecting comprises selection of monitoring procedures.

149. (previously presented) A method for providing a perioperative course of action to a clinician based on a patient's risk for complications during and after a surgical procedure associated with known genetic variations, comprising:

a) obtaining consent from a patient to obtain and assay a sample from a perioperative subject for genetic variations, said patient being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure;

b) obtaining said sample from said patient;

c) forwarding said sample to a clinical laboratory;

d) isolating DNA from said sample in said clinical laboratory;

e) subjecting said DNA to an assay in said clinical laboratory for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure;

f) forwarding the results of said genomic profile to said clinician;

g) directing said clinician to a perioperative course of action for said patient based on said risk for complications during and after said surgical procedure based on information from said genomic profile;

h) subjecting said patient to a surgical procedure based on said perioperative course action;

i) distributing said results of said patient's said genomic profile according to said patient's preference wherein said distributing is selected from the group consisting of destroying said results, saving said results for future access by said patient, saving said results for future access by said clinician, and donating said results for research; and

j) distributing said patient's said sample according to said patient's preference wherein said distributing is selected from the group consisting of destroying said sample, saving said sample for future access, and donating said sample for research.

150. (previously presented) The method of Claim 149, wherein said directing said clinician to said perioperative course of action comprises a computer program comprising instructions which direct a processor to analyze said results of said genomic profile.

151. (previously presented) The method of Claim 150, wherein said instructions translate said results into information of predictive value for a clinician.

152. (previously presented) The method of Claim 150, wherein said instructions translate said results into a risk assessment for treatment options.

153. (previously presented) The method of Claim 150, wherein said instructions translate said result into recommendations for treatment options.

154. (previously presented) The method of Claim 150, wherein said instructions generate a report for display to a clinician.

155. (previously presented) The method of Claim 154, wherein said display is in the form of a report that can be printed.

156. (previously presented) The method of Claim 154, wherein said display is in the form of a report on a computer monitor.

157. (previously presented) The method of Claim 150, wherein said instructions are sufficient to receive, process and transmit said results of said genomic profile to and from said patient, a clinical laboratory and medical personnel.

158. (previously presented) The method of Claim 157, wherein said transmission of said results uses an electronic communication system.

159. (previously presented) The method of Claim 158, wherein said electronic communication system transmits said results to a distant computer system for processing.

160. (previously presented) The method of Claim 150, wherein said instructions comprise information to optimize perioperative care that, based on at least the presence of variant alleles of two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNFα,* directs said clinician to a specific perioperative clinical pathway for said patient.

161. (previously presented) The method of Claim 149, wherein said perioperative course of action is an anesthesia treatment course of action.

162. (previously presented) The method of Claim 161, wherein said anesthesia treatment course of action is a general anesthesia course of action.

163. (previously presented) The method of Claim 162, wherein said general anesthesia treatment course of action is an inhalational anesthesia treatment course of action.

164. (previously presented) The method of Claim 162, wherein said general anesthesia treatment course of action is an intravenous anesthesia treatment course of action.

165. (previously presented) The method of Claim 162, wherein said general anesthesia treatment course of action is a combined inhalational and intravenous anesthesia treatment course of action.

166. (previously presented) The method of Claim 161, wherein said anesthesia treatment course of action is a regional anesthesia treatment course of action.

167. (previously presented) The method of Claim 161, wherein said anesthesia treatment course of action is a combined regional and general anesthesia treatment course of action.

168. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action is an anesthesia course of action during a medical procedure.

169. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action comprises selection of dosages of analgesic compounds.

170. (previously presented) The method of Claim 169, wherein said selection comprises increasing the dosage of analgesic compounds metabolized by CYP2D6.

171. (previously presented) The method of Claim 169, wherein said selection comprises decreasing the dosage of analgesic compounds metabolized by CYP2D6.

172. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action comprises prophylaxis for thrombosis.

173. (previously presented) The method of Claim 172, wherein said prophylaxis comprises increasing prophylaxis for thrombosis associated with variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS.*

174. (previously presented) The method of Claim 172, wherein said prophylaxis comprises decreasing prophylaxis for thrombosis associated with variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS.*

175. (previously presented) The method of Claim 149, wherein said perioperative course of action comprises monitoring procedures.

176. (previously presented) The method of Claim 149, wherein said perioperative course of action comprises pre-operative phenotypic tests and consultations.

177. (previously presented) The method of Claim 149, wherein said risk of complications provides a prognosis after an anesthesia treatment course of action.

178. (previously presented)The method of Claim 149, wherein said perioperative course of action is a surgical treatment course of action.

179. (previously presented) The method of Claim 178, wherein said surgical treatment course of action is a non-invasive surgical treatment course of action.

180. (previously presented) The method of Claim 178, wherein said surgical treatment course of action is an invasive surgical treatment course of action.

181. (previously presented) The method of Claim 149, wherein said risk of complications provides a prognosis after a surgical treatment course of action.

182. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action comprises a post-operative treatment course of action.

183. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action directs a clinician to a specific clinical pathway of medical intervention for said patient.

184. (previously presented) The method of Claim 149, wherein said perioperative treatment course of action directs a clinician to a specific clinical pathway of anesthesia intervention for said patient.

185. (previously presented)The method of Claim149, wherein said assay comprises structure-specific cleavage of oligonucleotide probes assay.

186. (previously presented) The method of Claim 149, wherein said subjecting said DNA to an assay further comprises:

i. providing a kit for generating a perioperative genomic profile for a subject, comprising:

a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS,* and *TNF*α so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and

b) a computer program on a computer readable medium comprising instructions which direct a processor to analyze data derived from use of said reagents; and

ii. generating said genomic profile with said kit.

187. (previously presented) The method of Claim 149, further comprising the step of encrypting said results of said genomic profile with privacy security protocols.

188. (previously presented) The method of Claim 149, further comprising the step of decoding said results of said genomic profile with privacy security protocols.

189. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile, wherein said markers are selected by the criteria of analytical validity, clinical validity and clinical utility;

c) selecting a perioperative course of action based on information from said genomic profile, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure;

e) distributing said results of said patient's said genomic profile according to said patient's preference wherein said distributing is selected from the group consisting of destroying said results, saving said results for future access by said paitent, saving said results for future access by said clinician, and donating said results for research; and

f) distributing said patient's said sample according to said patient's preference wherein said distributing is selected from the group consisting of destroying said sample, saving said sample for future access, and donating said sample for research.

190. (previously presented) The method of Claim 189, wherein said selecting of markers, said subjecting said sample to said assay, and said distributing of said results of said patient's said genomic profile is organized by an integrated electronic system.

191. (previously presented) The method of Claim 189, further comprising the step of selecting said genetic markers from the group consisting of genetic markers of pharmacogenetic risk, genetic markers of co-existing symptomatic conditions, genetic markers of co-existing non-symptomatic conditions, genetic markers of outcomes of a surgical procedure, genetic markers of a patient in a specific group, genetic markers that predict postoperative outcomes, and genetic markers consisting of unique genomic identifiers.

IX. EVIDENCE APPENDIX

#16
B. Webb
2/8/02

PATENT
Attorney Docket No. **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :	Kirk Hogan	
Serial No.:	09/613,887	Group No.: 1655
Filed:	07/11/01	Examiner: J.E. Goldberg
Entitled:	Methods and Compositions for Perioperative Genomic Profiling	

DECLARATION OF KIRK HOGAN, M.D. UNDER 37 CFR §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 2-8-02 By: Mary Ellen Waite
(Mary Ellen Waite

Madam:

1. I, Kirk Hogan, am the inventor of the subject matter embodied in the above-identified patent application.

2. I am a licensed and board-certified anesthesiologist, and am an Associate Professor in the Department of Anesthesiology at the University of Wisconsin Medical School.

3. As an instructor and licensed and board-certified practitioner, I am knowledgeable about the practice of anesthesiology.

4. Patients undergoing surgery and anesthesia exhibit wide variation in their physiologic and pathologic responses to drugs and trauma, such that an intervention that would be perfectly safe in one individual carries the potential for grievous harm and even death to another.

5. A substantial proportion of inter-individual variation is genetic, but, to my knowledge, prior to the present invention, this risk was unaccounted for in clinical practice by any technology, or by routine, direct molecular genetic analysis.

6. At present, to determine genetic risks before surgery, doctors ask if the patient has ever had a problem with anesthesia or surgery, and whether any of their family members have had a problem. This is the extent of the standard perioperative genetic evaluation unless an earlier record of perioperative care is available, in which case it is reviewed.

7. I am not aware of any case where physicians have carried out genomic profiling in the perioperative period using a heterogenous assay (other than my own work).

8. This is not surprising because the state of the art in the surgical and anesthetic arts at the time the application was filed teaches that perioperative genetic testing should not be conducted.

9. Even to this day, to my knowledge, perioperative genetic testing is not carried out.

10. In practice today, perioperative testing (even for biochemical testing) of healthy individuals is minimized or avoided. This is evidenced, for example, in a number of modern texts, manuals, and articles. For example, the 2002 Pediatric Anesthesia text by Gregory (attached) states that routine perioperative testing (biochemical tests) in healthy infants and children should be avoided. The 2002 Clinical Anesthesia Practice text by Kirby et al. (attached) states that routine testing for healthy individuals is unnecessary.

11. I filed a grant application entitled "Perioperative Genomic Profiles" with the Anesthesia Patient Safety Foundation (APSF), an organization dedicated to safety in the perioperative interval. The grant application described the subject matter of the present invention and was rejected. The review committee, consisting of experts in the field concerned with safety in the perioperative period, on 11/27/2000, explained that the invention goes in the opposite direction from the state of the art. The committee's comments, in full, are provided below:

> "The APSF committee members reviewing your proposal to study genomic profiles were impressed by the elegance of the proposal. It would take the issue

of patient safety in a new direction. It could improve the safety of the anesthetic experience, particularly for those patients with unknown diseases.

The committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the value equation the committee members considered the study might improve quality but the cost could be very high. As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be going in the opposite direction. It suggests we screen everyone in the hopes we find something on almost everyone. The direction of anesthetic evaluation is presently to *not* routinely do any preoperative studies.

The committee members were also concerned that patient confidentiality and ethics are problematic. Do patients want to know all that is potentially wrong with them? The committee members were concerned that the findings of the study could well increase costs with little benefit to the patient."

12. The review committees' comments demonstrate that experts in the field of perioperative medicine do not believe that perioperative genetic testing should be carried out—even after reading my grant proposal. It is clear to me, based on my knowledge and experience in the field, that they would also not believe perioperative genetic testing should be carried out in view of the references cited in the present Office Action (which they have reviewed by references in the grant application itself)—references that do not teach that perioperative testing should be carried out, and that do not provide guidelines for selecting markers useful for perioperative genetic testing.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 2/7/02 Signed: _____
Kirk Hogan

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	
Serial No.:	09/613,887	Group No.: 1634
Filed:	07/11/00	Examiner: J.A.. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**	

DECLARATION OF DOUGLAS BAIRD COURSIN, M.D. UNDER 37 C.F.R. §1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.o. Box 1450, Alexandria, VA 22313-1450

Dated: 6-11-07 By: _____
Mary Ellen Waite

Dear Madam:

I, Douglas Baird Coursin, M.D., do hereby declare as follows:

1. I received an M.D. in 1976 from Albany Medical College. I am a Diplomate of the National Board of Medical Examiners, the American Board of Internal Medicine, and the American Board of Anesthesiology with a Special Certificate of Competence in Critical Care Medicine. I am a Professor of Anesthesiology and Internal Medicine at the University of Wisconsin School of Medicine and Public Health. In 1996 – 1997, I served as President of the American Society of Critical Care Anesthesiologists. I've been an elected member of the Board of Directors of the American Board of Anesthesiology since 2001. I presently serve on the editorial boards of Current Opinions in Anaesthesiology, The Mayo Clinic Proceedings, and Critical Care Medicine. I am the 2006 recipient of the American Society of Critical Care Anesthesiologists Lifetime Achievement Award.

2. I understand that methodology for perioperative genomic profiles is disclosed and claimed in the patent application in connection with which this declaration is being submitted. The perioperative genomic profiles of the present patent application represent a completely novel approach that is not obvious in view of existing technologies. To my

knowledge, no one previously proposed or disclosed perioperative genomic profiles that would be successful in screening a patient perioperatively to determine a risk for multiple complications during a surgical procedure.

3. I have been in the practice of Anesthesiology and Critical Care Medicine for 26 years. During this entire time, and well before, the overriding mission of anesthesiologists, surgeons and other caregivers in the perioperative period has been to reduce the risk of adverse outcomes to the minimum for each patient. As well, it has long been recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery. Despite this heightened level of vigilance, and intense focus on a shared mission, no one taught or suggested perioperative genomic profiles before the present patent application.

4. Prior to the perioperative genomic profiles of the present patent application, surgeons and anesthesiologists were highly motivated to detect multiple risks for complications during a surgical procedure associated with genetic variations. For example, every patient is asked whether any family members may have had complications with surgery and anesthesia, and the patient's answer is recorded on a pre-operative checklist. Nevertheless, those of ordinary skill in the art *i.e.*, anesthesiologists and surgeons, did not arrive at the solution of the presently claimed invention. Thus, the perioperative genomic profiles of the present patent application clearly fulfill a long felt, but hitherto unmet need.

5. I have participated in a recently completed NIH-funded, prospective, multi-center investigation in which perioperative genomic profiles including alleles in *BChE, CYP2D6, MTHFR, MTR, MTRR, CBS, FII, FV, B 2AR, HBB, ApoE, MYH7, FII, FV, TPMT, CCR5, TNF a , TNF b , CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, ABC, ACE, Gender,* and *ABO*, were generated in 450 patients undergoing surgery using the technology described in the present patent application. This NIH grant focused upon the long felt but unmet needs in detection of genetic susceptibilities in the time before, during and after surgery and anesthesia.

6. Surprisingly, even after polymorphisms in non-pathogenic alleles (*i.e.*, the ABO blood group and gender-specific alleles) were withdrawn from analysis, 391 of 450 patients were found to be mutant homozygotes at 1 or more loci, with a mean number of 2 mutant homozygous loci per patient. In turn, a mean of 11 mutant alleles in aggregate (*i.e.*, homozygous plus heterozygous mutant polymorphisms) per patient were observed at loci comprising the perioperative genomic panel. These unexpected results demonstrate that significant genetic heterogeneity is present in most patients in advance of surgery that is not accounted for using contemporary tools for detection, *e.g.*, a family history check-box. Without question, the perioperative genomic profiles of the present patent application will avoid many deleterious outcomes, and save lives.

7. I am aware that the perioperative genomic profiles of the present patent application have been considered obvious by the United States Patent Office in the light of numerous separate references brought together for the first time in the present application. However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary

practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made.

The undersigned declares further that all statements made herein of his own knowledge are true, and all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are so made punishable by fine or imprisonment, or both, under §101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: June 10th, 2007 Signed: _____
Douglas Baird Coursin M.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan		
Serial No.:	09/613,887	Group No.:	1655
Filed:	July 11, 2000	Examiner:	J.E. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**		

SECOND DECLARATION OF KIRK HOGAN, M.D. UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: July 8, 2002 By: Susan M. McClintock
Susan M. McClintock

Madam:

1. I, Kirk Hogan, am the inventor of the subject matter embodied in the above-identified patent application.

2. I am not aware of any case where physicians have carried our genomic profiling in the perioperative period using a heterogenous assay (other than my own work).

3. Even to this day, to my knowledge, the ordinary artisan does not clearly recognize the benefit of testing an individual for genetic markers prior to surgery in order to generate a perioperative genomic profile.

4. This is evidenced, for example, in the 2002 manuscript "Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation."

5. To prepare the Practice Advisory the 12 member Task Force used a six step process. First, they reached consensus on the criteria for evidence of effectiveness of preanesthesia evaluation. Second, original published research studies relevant to these issues were reviewed. Third, consultants who had expertise or interest in preanesthesia evaluation, and who had practiced or worked in various settings (e.g., academic and private practice) were asked to (1) participate in opinion surveys on the effectiveness of various preanesthesia evaluation strategies, and (2) review and comment on the draft reports of the Task Force. Fourth, opinions about various elements of this Practice Advisory were solicited from a random sample of active members of ASA. Fifth, the Task Force held several open forums at major national anesthesia meetings to solicit input on key concepts of this Advisory. Sixth, all available information was used to build a consensus within the Task Force on the Advisory.

6. The Task Force concludes "*Routine preoperative tests* (*i.e.*, tests intended to discover a disease or disorder in an asymptomatic patient) do not make an important contribution to the process of perioperative assessment and management of the patient by the anesthesiologist." (emphasis in original)

7. The Task Force Practice Advisory for Preanesthesia Evaluation does not teach that perioperative genetic testing should be carried out.

8. The Task Force Practice Advisory for Preanesthesia Evaluation does not provide guidelines for selecting markers useful for perioperative genetic testing.

9. The Task Force Practice Advisory for Preanesthesia Evaluation does not advocate, consider or even mention genetic testing, use of genetic markers, or generation of genomic profiles in the perioperative interval.

10. The Task Force Practice Advisory for Preanesthesia Evaluation demonstrates that both experts and artisans of ordinary skill in the art do not believe, or clearly recognize, that perioperative genetic testing should be carried out.

11. The ordinary artisan did not clearly recognize the benefit of testing an individual prior to surgery and subjection to anesthesia for known genetic markers associated with conditions triggered by anesthesia or surgery at the time the invention was made.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be

true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 7/8/02 Signed: K Hogan

Kirk Hogan

X. RELATED PROCEEDINGS APPENDIX

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIRK HOGAN

Appeal No. 2006-1560
Application No. 09/613,887

ON BRIEF

Before ADAMS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of screening patients for risk of surgical complications, which the examiner has rejected a obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm the rejection.

Background

"Although surgery saves many lives, surgical complications result in many instances of mortality and morbidity. Complications related to surgery and anesthesia include infections, excessive blood loss, thrombosis, nausea and vomiting, and anesthesia reactions." Specification, page 1.

"One anesthesia-related complication is malignant hyperthermia (MH). MH is an autosomal dominant trait that causes a severe, uncontrollable fever when anesthesia is administered." Id. "[M]uscle relaxants commonly given in conjunction with anesthesia, such as succinylcholine or mivacurium, can cause prolonged paralysis and apnea in a patient after the patient has awoken from anesthesia. The paralysis, caused by mutations in the butyrylcholinesterase gene (BChE), is inherited as an autosomal recessive trait.. . . In addition, subjects with mutations in Cytochrome P450 enzymes . . . can have adverse reactions due either to the inability to activate or metabolize certain drugs (e.g., morphine derivatives and anti-dysr[hy]thmics). Complications can be avoided by substituting other medications or adjusting dosage." Page 2.

Despite these known, genetically determined susceptibilities to side effects of anesthesia, however, "the current state of the surgical field is to reduce or eliminate perioperative testing." Specification, page 5. "[T]he current procedure is simply to ask a patient if they have had any previous difficulties with anesthesia or surgery. . . . The use of laboratory tests for relatively healthy patients has generally been reduced or eliminated. Reasons for elimination include the cost of screening tests, inaccuracy and lack of specificity, [and] uncertainty as to how to alter treatment course of action in response to results." Id.

The specification discloses "methods for perioperative genomic screening of subjects, in particular . . . perioperative screening for markers indicative of responses to anesthesia and other perioperative or operative treatments and procedures." Page 3. "Markers for inclusion are selected for their accuracy, specificity, and predictive value. The perioperative profiles . . . allow for the individualization of treatment options for each

subject." Page 6. "Markers are also selected for which the course of action can be altered in a time and cost effective way to eliminate or reduce unwanted surgical complications. For example, a practitioner may cho[o]se a particular anesthetic or analgesic in order to avoid a life-threatening response." Id.

Discussion

1. Claim construction

Claims 74-105 are pending and on appeal. Claim 74 is representative and reads as follows:

74. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample form a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complication during said surgical procedure.

"It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Sneed, 710 F.2d 1544, 1548, 218 USPQ 385, 388 (Fed. Cir. 1983) (citation omitted).

In addition, "while it is true that claims are to be interpreted in light of the specification and with a view to ascertaining the invention, it does not follow that

limitations from the specification may be read into the claims." Sjolund v. Musland, 847 F.2d 1573, 1581, 6 USPQ2d 2020, 2027 (Fed. Cir. 1988) (emphasis in original). On the contrary, "the claims define the invention. . . . [L]imitations from the specification are not to be read into the claims." Id. at 1582, 6 USPQ2d at 2027.

Here, claim 74 is directed to a method the comprises obtaining a sample from a patient and testing the sample for the presence of "two or more nucleic acid genetic markers in two or more genes associated with two or more conditions." The results of the testing form the basis for "determining a risk for complications during said surgical procedure"; thus, the "conditions" recited in the claim are those associated with "a risk for complications during a surgical procedure associated with known genetic variations," as recited in the preamble.

Claim 74 also states that the results of the "assay for detecting two or more nucleic acid genetic markers . . . generate[s] a genomic profile." The specification states that "a 'genomic profile' refers to a set of information about a given 'subject's' genes (e.g., the presence or absence of a specific set of mutations or 'SNPs')." Page 23, lines 7-9. Thus, the "genomic profile" recited in claim 74 merely refers to the data resulting from the recited "assay for detecting two or more genetic markers."

Claim 74 also states that the genomic profile is "for use in selecting a perioperative course of action." This claim language, however, merely recites an intended use for the data resulting from the assay step in the claim. "An intended use or purpose usually will not limit the scope of the claim because such statements usually do no more than define a context in which the invention operates." Boehringer Ingelheim Vetmedica v. Schering-Plough Corp., 320 F.3d 1339, 1345, 65 USPQ2d

1961, 1965 (Fed. Cir. 2003). Therefore, claim 74 is not limited to a process that includes selecting a perioperative course of action based on the results of the assay.

2. Obviousness

The examiner rejected claims 74-105 under 35 U.S.C. § 103 as obvious in view of Miller,[1] Quane[2] or AAS,[3] La Du[4] or Pharmacogenetics,[5] Evans[6] or Poort,[7] Hoon,[8] and Hacia.[9]

The examiner characterized Miller as teaching "screening a patient preoperatively to determine a risk for complications during a surgical procedure," although she acknowledged that Miller does not teach testing for "two or more known genetic variations associated with two or more conditions." Examiner's Answer, page 4.

However, the examiner cited Quane for its disclosure of "novel common mutations in [the] ryanodine receptor gene (RYR1) in malignant hyperthermia (MH)" and noted that Quane teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." Id. The examiner

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[1] Anesthesia, Vol. 2, Miller (ed.), pp. 1323-1333, Churchill Livingstone, NY (1981)
[2] Quane et al., "Detection of a novel common mutation in the ryanodine receptor gene in malignant hyperthermia: implications for diagnosis and heterogeneity studies," Human Molecular Genetics, Vol. 3, pp. 471-476 (1994)
[3] La Du, "Butyrylcholinesterase variants and the new methods of molecular biology," Acta Anaesthesiologica Scandinavica, Vol. 39, pp. 139-141 (1995)
[4] La Du et al., "Proposed nomenclature for human butyrylcholinesterase genetic variants identified by DNA sequencing," Cellular and Molecular Neurobiology, Vol. 11, pp. 79-89 (1991)
[5] The reference is cited as "Pharmacogen[e]tics, Chapter 4, pp. 309-326" in the Information Disclosure Statement received April 6, 2001 (reference number 202 in the IDS).
[6] Evans et al., "Pharmacogenomics: Translating functional genomics into rational therapeutics," Science, Vol. 286, pp. 487-491 (1999)
[7] Poort et al., "A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis," Blood, Vol. 88, pp. 3698-3703 (1996)
[8] Hoon et al., U.S. Patent 6,057,105, issued May 2, 2000.
[9] Hacia, "Resequencing and mutational analysis using oligonucleotide microarrays," Nature Genetics Supplement, Vol. 21, pp. 42-47 (1999)

also cited AAS for its disclosure that certain variants of the butyrylcholinesterase (BChE) gene cause patients to react differently to the muscle relaxant drug succinylcholine. Id. The examiner also noted AAS's advice that anesthesiologists need to keep up to date about the application of molecular biology tests to BChE variants. Id.

The examiner cited La Du, Pharmacogenetics, and Evans as disclosing genetic variations that are associated with abnormal responses to drugs. See the Examiner's Answer, pages 6-7:

> La Du . . . teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. . . .
>
> Pharmacogenetics teaches polymorphisms of desbrisoquine [sic] hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. . . . Codeine is [an] ineffective analgesic in the 5-10% of the population who have a PM [poor metabolizer] phenotype.
>
> Evans . . . teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. . . . Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. . . ."

The examiner cited Poort's disclosure that a "20210 AG gen[ot]ype of the prothrombin gene . . . is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedure or trauma." Id., page 7. Finally, the examiner cited Hoon as "teach[ing] the benefits of using multiple markers in detection assays," id., and Hacia as "teach[ing] mutational analysis using oligonucleotide microarrays . . . allow[ing] for unprecedented throughput in mutational analysis with a high degree of accuracy." Id., page 8.

We agree with the examiner that the cited references would have made the method of claim 74 prima facie case obvious. In particular, Quane, AAS and Pharmacogenetics disclose specific mutations that are associated with abnormal responses to commonly used drugs, and which can be identified in patients by genetic analysis.

Quane teaches that malignant hyperthermia (MH) is a potentially fatal complication "triggered in susceptible people by all commonly used inhalation anaesthetics" (abstract), that susceptibility to MH can be predicted by testing strips of muscle tissue in vitro, and that "[o]nce an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided" (page 471, right-hand column).

Quane also discloses that certain mutations in the ryanodine receptor gene (RYR1) are associated with susceptibility to MH: "a point mutation . . . that results in an Arg to Cys substitution at position 615 . . . has been found in 3-5% of human MH families investigated and is the most common MHS [MH susceptible; see page 471, right-hand column] mutation known to date. More recently, we reported a second MHS mutation, namely an Arg to Cys substitution at position 163 which accounts of 2-3% of MHS cases." Paragraph bridging pages 471-472 (reference numbers omitted). Quane reports that another mutation, Gly341Arg, "accounts for approximately 10% of Caucasian MHS cases." Abstract. Finally, Quane states that the Gly341Arg mutation "satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means." Page 474, left-hand column.

AAS teaches that genetic variation in the butyrylcholinesterase (BChE) gene causes patients to react differently to the muscle relaxant succinylcholine: "[T]he better known variants [are known as] A=atypical (dibucaine resistant), F=fluoride resistant, and S=silent (no significant activity)." Page 139, right-hand column. AAS states that succinylcholine (SC) is metabolized quickly in normal patients, so that in patients lacking functional BChE, the standard dose "represents an enormous overdosing" and is "potentially toxic." Page 139, left-hand column.

AAS also teaches that "[a]bout 16 different DNA mutations causing the silent phenotype have been uncovered, so far" (page 140, left-hand column, first full paragraph) and that "[w]e have been able to sequence the entire BCHE coding region and consider all the possible structural mutations using PCR amplification" (page 140, end of the paragraph bridging the columns). Finally, AAS notes that "the principles of molecular biology and their application to BChE variants [have been] well illustrated . . ., and anesthesiologists need to keep up to date about these applications. Other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years." Paragraph bridging pages 140 and 141.

Pharmacogenetics teaches that the enzyme cytochrome P4502D6 (also known as CYP2D6) is involved in biotransformation of the antihypertensive agent debrisoquine and "at least 30 other agents." Page 310, first and last paragraphs. "[A]pproximately five to ten percent of the individuals in healthy Caucasian populations are distinguishable as phenotypically 'poor metabolizers' (PM)." Page 310, left-hand column, first paragraph. "Codeine and encainide represent examples of drugs that

require metabolic activation by CYP2D6 before certain of their therapeutic effects can be fully realized. Thus, for these drugs it is the PM subjects who may experience therapeutic failure. . . . [C]odeine is therefore an ineffective analgesic in the 5 to 10 percent of the population who have the PM phenotype." Page 317, left-hand column, first full paragraph.

Pharmacogenetics also discloses "the development of rapid and specific PCR-based allele-specific amplification tests to detect the presence of the D6-A and D6-B mutant alleles, and more recently the putative D6-C allele. By combining these with the . . . XbaI RFLP analysis, about 95 percent of all mutant alleles of CYP2D6 could be identified, allowing for the prediction of over 90 percent of PM phenotypes." Page 314, right-hand column, first full paragraph.

Evans and Hacia discuss methods of genetic analysis. Evans states that "[s]ince the cloning and characterization of CYP2D6, human genes involved in many such pharmacogenetic traits have been isolated, their molecular mechanisms have been elucidated, and their clinical importance has been more clearly defined. . . . [T]he overall pharmacologic effects of medications are typically not monogenic traits; rather, they are determined by the interplay of several genes encoding proteins involved in multiple pathways of drug metabolism, disposition, and effects." Page 487, paragraph bridging the columns. Evans provides a list of "[e]xamples of clinically relevant genetic polymorphisms influencing drug metabolism and effects." Table 1.

Evans also discloses that "technology will soon make it feasible to use molecular diagnostics to more precisely select medications and dosages that are optimal for individual patients. In this regard, automated systems are being developed to

determine an individual's genotype for polymorphic genes that are known to be involved in the pathogenesis of their disease, in the metabolism and disposition of medications, and in the targets of drug therapy." Paragraph bridging pages 490 and 491. Evans provides an example of a DNA array for the "detection of functionally important mutations in genes that are important determinants of drug effects"; the exemplified array includes "genes that could influence a patient's response to chemotherapy for acute lymphoblastic leukemia." See Figure 3.

Hacia states that "[o]ligonucleotide array-based detection of known genomic DNA sequence variations was first reported in 1989. . . . Advanced oligonucleotide array manufacturing processes have opened the way to evaluating more complex systems. Arrays of 1,480 oligonucleotide probes . . . were designed to detect 37 known mutations in the coding region of CFTR, as well as all possible single-nucleotide substitutions." Page 42, right-hand column. Hacia also teaches that "[a]mong the greatest strengths of array-based mutational analysis is the ability to detect specific sequence changes of interest. Once specific hybridization patterns or 'signatures' of large numbers of mutant alleles of interest are known, it will be possible to search for those signatures in many different samples simultaneously." Page 45, right-hand column.

We agree with the examiner that these disclosures, viewed collectively by a person of ordinary skill in the art, would have made obvious the method defined by claim 74.[10] That is, it would have been obvious to a person of skill in the art to test a patient who was scheduled for surgery to determine whether the patient had any of the

[10] In our view, the other references cited by the examiner are essentially cumulative to those discussed above.

genetic polymorphisms known to be associated with specific surgery- or anesthesia-related complications, including the RYR1 mutations discussed by Quane, the BChE mutations discussed by AAS, and the CYP2D6 mutations discussed by Pharmacogenetics. The skilled artisan would have found it obvious to conduct such testing (using, for example, DNA hybridization techniques such as those disclosed by Evans and Hacia) in order to avoid the known risk of side-effects, including death, that were likely to occur when patients having a particular genetic make-up were given particular drugs.

Appellant argues that the examiner has not adequately established that a person of ordinary skill in the art would have been motivated to combine the teachings of the cited references. See the Appeal Brief, pages 15-21. Appellant's argument, however, focuses on the teachings of Quane in isolation. A proper obviousness analysis must consider all of the teachings of the prior art, viewed from the perspective of a person of ordinary skill in the art. For the reasons discussed above, we conclude that the references cited by the examiner would have suggested the method of claim 74 to those of ordinary skill in the art.

Appellant also argues that he has provided evidence that rebuts the reasoning relied on by the examiner by showing that "ordinary artisans did not agree with the Examiner's suppositions regarding the obviousness of perioperative genomic profiles." Appeal Brief, page 22. Appellant argues that the APSF Grant Review[11] is evidence of

[11] Appellant states in the declaration filed under 37 CFR § 1.132 on February 8, 2002, that he "filed a grant application entitled 'Perioperative Genomic Profiles' with the Anesthesia Patient Safety Foundation (APSF). . . . The grant application described the subject matter of the present invention and was rejected." ¶ 11. Neither the grant application nor the rejection letter appear to be in the record, although

the nonobviousness of the claimed method, because skilled artisans described it a "tak[ing] the issues of patient safety in a new direction," and stated that "[t]he direction of anesthetic evaluation is presently to not routinely do any preoperative studies." Appeal Brief, page 23.

Appellant argues that Gregory[12] and Kirby[13] teach away from the claimed method in their statements that "routine screening tests are of little value" (Gregory) and "[t]here are abundant data supporting the concept that routine laboratory screening tests are not cost-effective in the asymptomatic patient" (Kirby). Appeal Brief, page 24.

Appellant also argues that Hopkins[14] is evidence that "the Examiner's premises concerning the motivations of the ordinary artisan are in clear error," in that Hopkins states that "[t]he complexity of the molecular genetics of MH described above precludes DNA-based diagnosis at present." Appeal Brief, page 26.

Finally, Appellant argues that his second declaration under 37 CFR § 1.132 (dated July 15, 2002) and the reference attached thereto,[15] are evidence of nonobviousness, in that the "Practice Advisory for Preanesthesia Evaluation . . . does not provide guidelines for selecting markers useful for perioperative genetic testing, and does not advocate, consider or even mention genetic testing, use of genetic markers, or generation of genomic profiles." Appeal Brief, page 27.

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we will accept Appellant's statement that the quotation in ¶ 11 of the declaration represents "the committee's comments, in full."

[12] Gregory, Pediatric Anesthesia, 4th edition, Churchill Livingstone, NY (2002). Page 184 of Gregory was attached to the declaration filed Feb. 8, 2002.

[13] Kirby et al., Clinical Anesthesia Practice, 2nd edition, W.B. Saunders Co., Philadelphia (2002). Page 12 of Kirby was attached to the declaration filed Feb. 8, 2002.

[14] Hopkins, "Malignant hyperthermia: advances in clinical management and diagnosis," Br. J. of Anaesthesia, Vol. 85, pp. 118-128 (2000)

[15] "Practice Advisory for Preanesthesia Evaluation," Anesthesiology, Vol. 96, pp. 485-496 (2002)

Appellant concludes that "this factual evidence consistently documents that at the time the invention was made, ordinary artisans did not agree with the Examiner's suppositions regarding the obviousness of perioperative genomic profiles." Appeal Brief, page 22.

While we appreciate Appellant's effort to provide evidence supporting his position, we agree with the examiner that the evidence does not overcome the prima facie case of obviousness. The APSF committee's response to Appellant's grant application is not probative of nonobviousness for two reasons. First, the grant application itself is not in the record, so we do not know how the method that was proposed in the grant, and addressed in the committee's comments, compares to the method of claim 74.

Second, and more important, the committee's comments were addressed to the cost-effectiveness of whatever method was proposed in the grant. According to Appellant's declaration (¶ 11), the committee stated that

> [T]he committee members considered the study might improve quality but the cost could be very high. As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be going in the opposite direction.

However, whether a claimed invention would have been obvious in the § 103 sense has little to do with whether it would be economically viable in actual practice. A method can properly be considered obvious under § 103 even if it would have been more expensive than alternative methods. See In re Farrenkopf, 713 F.2d 714, 718, 219 USPQ 1, 4 (Fed. Cir. 1983):

> That a given combination would not be made by businessmen for economic reasons does not mean that persons skilled in the art would not

> make the combination because of some technological incompatibility. Only the latter fact would be relevant.

(Citing Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1013, 217 USPQ 193, 200 (Fed. Cir. 1983).)

In this case, a person of ordinary skill in the art would have found it obvious, in view of the cited references, to test a patient for genetic markers in order to avoid known surgery- and anesthesia-related complications, even though such tests might be expensive, because those skilled in the art would have recognized that the tests were useful for diagnosing patients who were likely to suffer complications if given certain drugs.

The Kirby and Gregory textbooks also do not persuade us that the examiner's rejection is in error. The textbooks suffer from the same deficiency as the APSF committee's remarks. In addition, both textbooks address only "routine laboratory screening tests," which appear to be limited to tests such as urinalysis, hemoglobin and hematocrit. See Gregory, page 184, left-hand column. Neither reference addresses tests for genetic markers such as claimed here.

Hopkins also does not overcome the prima facie case of obviousness. It is true that Hopkins states that the "complexity of the molecular genetics of MH described above precludes DNA-based diagnosis at present [i.e., in 2000]." Nevertheless, Hopkins also states that known mutations were found in a number of MH-susceptible individuals and that "it is difficult to envisage that the mutations so far described in RYR1 do not play a role in MH." Page 125, left-hand column. In any event, Hopkins at best expresses doubt about the likelihood of successfully diagnosing malignant

hyperthermia, but it says nothing to raise doubts about genetic testing for the CYP2D6 or BChE mutations that are disclosed by Pharmacogenetics and AAS, respectively.

Finally, with respect to Appellant's rebuttal evidence, the Practice Advisory attached to Appellant's second declaration suffers from a combination of the deficiencies discussed above: it reflects the cost-benefit trade-offs of the standard of care for present-day clinical practice, which is the wrong standard for determining obviousness under § 103, and it is limited to routine laboratory tests that do not include the type of genetic testing at issue in this case.

Appellant also argues that the cited references do not teach or suggest all of the limitations of claims 74, 76, 78, 81-87, 91-94, 96, 98, 101-103, or 105. Appeal Brief, pages 12-14 and 29-30. However, we agree with the examiner that the cited references would have suggested the limitations of these claims, for the following reasons.

Appellant argues that the references cited by the examiner "fail to teach, suggest or even mention" the following limitations: from claim 74, "a genomic profile for use in selecting a perioperative course of action"; from claim 87, "a genomic profile for use in selecting a surgical treatment course of action"; from claims 94 and 101, "a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure"; and from claim 102 "an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said assay results are consulted in selecting an appropriate anesthesia treatment." Appeal Brief, pages 12-13.

We do not agree with Appellant that these claim limitations distinguish the claimed methods from that suggested by the prior art. With respect to claims 74, 87,

94, and 101, the "genomic profile . . ." claim language merely recites an intended use for the information that is produced during the claimed process. The intended use of the data does not limit the claimed process. See pages 4-5 above.

Claim 102 is somewhat different, in that it recites a step of "subjecting said subject to a surgical procedure, wherein said assay results are consulted in selecting an appropriate anesthesia treatment for said subject." Thus, claim 102 requires considering the assay results during the selection of anesthesia for a patient undergoing surgery. This limitation is suggested by the cited references. For example, Quane states that a Gly341Arg mutation in the RYR1 gene causes sensitivity to malignant hyperthermia, and that "[o]nce an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." These disclosures would have reasonably suggested consulting the results of an assay for the RYR1 Gly341Arg mutation and avoiding anesthetics that trigger MH in patients having that mutation. Appellant's argument with respect to claims 86, 98, 103, and 105 (Appeal Brief, page 14) is unpersuasive for the same reason.

Appellant argues that the cited references do not teach or suggest assaying for "5 or more mutations," as recited in claims 84, 92, and 99, or "10 or more mutations," as recited in claims 85, 93, and 100. Appeal Brief, pages 12-13. Appellant also argues that the cited references do not suggest assaying for mutations in at least two of the specific genes recited in claims 83, 91, and 101. See id., pages 12, 13, and 30.

We do not find this argument persuasive. Quane discloses three mutations in the RYR1 gene that are associated with MH susceptibility: Arg to Cys at position 615 (paragraph bridging pages 471 and 472), Arg to Cys at position 163 (id.), and

Gly341Arg (abstract). Pharmacogenetics discloses at least three mutations associated with the "poor metabolizer" phenotype of CYP2D6 (the D6-A, D6-B, and D6-C alleles; page 314, right-hand column). AAS discloses that "about 16 different DNA mutations causing the silent phenotype have been uncovered" (page 140, first full paragraph), along with one causing the "atypical" phenotype and two causing the "fluoride-resistant phenotype" (page 140, second full paragraph).

Based on these disclosures, the skilled artisan would have found it obvious to assay for each of these mutations, which were known to be associated with aberrant drug responses. Thus, those skilled in the art would have found it obvious to assay for at total of at least ten mutations in the RYR1, BChE (butyrylcholinesterase), and CYP2D6 (debrisoquine hydroxylase) genes.

Appellant argues that the cited references do not teach or suggest the added limitations of claim 76, 78, and 96. Appeal Brief, pages 13 and 14. These claims, however, merely further limit the intended use of the information that is produced during the claimed process. Since the intended use of the data does not limit the claimed process (see pages 4-5 above), the language recited in claims 76, 78, and 96 does not distinguish the claimed methods from that suggested by the prior art.

Finally, Appellant argues that the cited references do not teach or suggest a "genomic profile [that] comprises a presymptomatic diagnosis," as recited in claim 81. Appeal Brief, page 13. This argument is also unpersuasive. As discussed above (page 4), the "genomic profile" recited in claim 74 is merely the data resulting from the recited "assay for detecting two or more genetic markers." An assay for the specific mutations disclosed in the cited references would inherently be diagnostic of, among other things,

a potential for an abnormal response to succinylcholine. As AAS states, the "genetically-determined prolonged response to SC in occasional patients is a classical example of a pharmacogenetic condition. Since these individuals . . . [do not] suffer any adverse consequences of this hereditary condition, unless SC or mivacurium is given, the condition is provoked only when the offending drug substances are administered." Page 139, left-hand column. Thus, a presymptomatic diagnosis is suggested by at least AAS.

Summary

The examiner has made out a prima facie case of obviousness, which Appellant has not effectively rebutted. The examiner's rejection is supported by a preponderance of the evidence in the record and is therefore affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Donald E. Adams)
Administrative Patent Judge)
)
)
Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Lora M. Green) INTERFERENCES
Administrative Patent Judge)
)

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIRK HOGAN

Appeal No. 2006-1517
Application No. 09/976,423

ON BRIEF

Before BARRY, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to kits for determining risk of surgery- or anesthesia-related complications. The examiner has rejected the claims as based on new matter, anticipated, and obvious in view of the prior art. We have jurisdiction under 35 U.S.C. § 134. We reverse all of the rejections.

Background

"Although surgery saves many lives, surgical complications result in many instances of mortality and morbidity. Complications related to surgery and anesthesia include infections, excessive blood loss, thrombosis, nausea and vomiting, and anesthesia reactions." Specification, page 1.

Mutations in several genes have been linked to increased risk of surgery- and anesthesia-related complications including malignant hyperthermia, sepsis, and possible toxicity of anesthetics and other drugs. See page 2, lines 3-4 and 22-24; page 2, line 27 to page 3, line 2; and page 3, lines 12-13.

The specification discloses "a kit for generating a perioperative genomic profile for a subject, comprising a reagent capable of detecting the presence of a variant allele of two or more genes markers [sic] selected from [particular genes]; and instructions for using the kit for generating the perioperative genomic profile for the subject." Page 6, lines 15-20.

"In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP [single nucleotide polymorphism; page 28, line 19] or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease). . . . Thus, . . . the clinician, who is not likely to be trained in genetics or molecular biology, need not understand the raw data of the genomic profile. The data is presented directly to the clinician in its most useful form." Page 50, lines 8-17.

"For example, in some embodiments . . . , a sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo. The genomic profile data is then prepared in a format suitable for

interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options." Page 50, line 22, to page 51, line 10.

Discussion

1. Claim construction

Claims 72-107 are pending and on appeal. Claims 72 and 106 are representative and read as follows:

> 72. A kit for generating a perioperative genomic profile for a subject, comprising:
>
> a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and
>
> b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.
>
> 106. A perioperative genomic profile kit having component parts configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRRR, CBS, TNFα and TNFβ, so as to generate a genomic profile for use in selecting a perioperative course of action for said subject and thereby providing a subject-specific clinical pathway for said subject, comprising information to optimize perioperative care that, based at least on the presence or absence of said variant alleles of two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

Thus, claim 72 is directed to a kit comprising "reagents" and "a computer program." The claim specifies that the reagents in the kit are "configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, . . . [they] are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from [a group of specific genes]."

As we interpret the claim language, it requires reagents that are sufficient to detect the presence or absence of variant alleles in at least two of the recited genes when exposed to a sample containing a target nucleic acid. That is, the reagents in the kit can be combined with a sample from a perioperative subject and processed to detect the presence of variant alleles in the specified genes, without the addition of other reagents. This interpretation is required by the claim language: if reagents not included in the kit were required to detect the presence of variant alleles in the recited genes, then the kit would not comprise reagents "sufficient to detect" those alleles.

The other passages in part (a) of claim 72 do not constitute limitations of the claimed kit. The passage stating that the "subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure" recites nothing more than an intended use of the claimed kit. That is, the specification states that the kit is intended to be used shortly before or during surgery (see page 9, lines 3-11) but that intended use does not limit the components of a kit: the same components would be required to detect the presence of the recited alleles regardless of whether the kit was used perioperatively.

In addition, the passage stating that the reagents "generate a genomic profile for use in selecting a perioperative course of action for said subject," merely recites the intended outcome of using the regents. The specification defines "genomic profile" as "a set of information about a given 'subject's' genes (e.g., the presence or absence of a specific set of mutations or 'SNPs')." Page 27, lines 13-14. Thus, the "genomic profile" recited in the claims refers simply to the data showing the presence or absence of the recited variant alleles, and reagents that are sufficient to detect alleles in at least two of the recited genes are therefore, by definition, capable of generating a genomic profile.

Finally, the kit defined by claim 72 comprises "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents."

Claim 106 is similar to claim 72 in that it requires the same reagents (which are termed "component parts" in claim 106). As with claim 72, the claim language stating that the "subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure" recites nothing more than an intended use of the claimed kit, and does not further limit the claim. Likewise, the recitation "so as to generate a genomic profile" also does not further limit the claim, because detecting the presence or absence of alleles in at least two of the recited genes by definition generates a genomic profile.

Finally, the claim language following "so as to generate a genomic profile" recites nothing more than the intended use of the genomic profile that is to be generated by the kit, and does not further limit the claimed kit. That is, the kit requires regents ("component parts") sufficient to detect polymorphisms in at least two of the recited genes, thereby generating a genomic profile, but the reagents that are capable of

detecting those alleles are the same regardless of whether the resulting genomic profile is used as recited in claim 106; the intended use language at the end of the claim therefore does not constitute a structural limitation of the claimed kit.

Claim 106 differs from claim 72 in that it does not require the claimed kit to comprise a computer program in addition to the component parts that detect the presence of variant alleles.

2. Written Description

The examiner rejected claims 72-105 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description; that is, being based on new matter. The examiner argued that "the specification does not describe or discuss 'a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents." Examiner's Answer, paragraph bridging pages 3 and 4. See also page 6: "The concept of 'a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents' does not appear to be part of the originally filed invention."

However, on page 4 of the Examiner's Answer, the examiner quotes the following passage from the specification: "In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease)" (emphases added). While this passage does not use precisely the same words as claim 72, we agree with Appellant that it reasonably describes the limitation recited in the claim.

The examiner also rejected the claims because "[t]here is no disclosure in the instant specification of a kit comprising reagents and a computer program." Examiner's Answer, page 4. See also page 5 ("there are no teachings of a computer program within a kit").

Again, however, we agree with Appellants that the specification describes the combination of a computer program and allele-detecting reagents, although not precisely in the terms used in the claims. The specification describes kits comprising reagents capable of detecting variant alleles of various genes (see, e.g., page 6, lines 15-20) and describes a "computer-based analysis program . . . to translate the raw data" generated by such kits (page 50, lines 8-12).

Moreover, the specification states that "Figure 2 illustrates the transformation of a sample . . . into data useful for the clinician." Page 50, lines 21-22. "[A] sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo." Page 50, line 22 to page 51, line 7.

The specification also contemplates that the party generating the genomic profile from the sample will process the data into a more easily understood format. See page 51, lines 8-15: "The genomic profile data is then prepared in a format suitable for interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options. . . . [I]n some embodiments, the genomic profiling service generates a report

that can be printed for the clinician . . . or displayed to the clinician on a computer monitor."

In our view, these disclosures reasonably support the concept of combining reagents for detecting variant alleles with a computer program to analyze data indicating the presence or absence of such variant alleles. Adequate written description does not require literal support in the specification: "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue." Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Adequate written description requires only a disclosure that conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. See id.

In this case, we conclude that the examiner has not adequately explained why the description provided by the specification would be considered inadequate, by those skilled in the art, to show possession of the instanty claimed kit. We therefore reverse the rejection based on the first paragraph of 35 U.S.C. § 112.

3. Anticipation

The examiner rejected claims 72-105 under 35 U.S.C. § 102(b) as anticipated by Applied Biosystems,[1] and rejected claims 106 and 107 as anticipated by Perkin Elmer.[2]

With regard to Applied Biosystems, the examiner reasoned that

> Applied Biosystems provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. Applied Biosystems products for sale include: a DNA analysis system; software for genetic analysis; . . . PRISM Ready reaction

[1] Sales catalog of Applied Biosystems, Inc., pp. 135-157 and 160-164 (1993)
[2] PCR Systems, Reagents & Consumables catalog, Perkin Elmer, pp. 15-18 (1995)

> cycle sequencing kits; AmpliTaq Cycling Sequencing Kits; . . . etc. Each of these products is capable of detecting the presence of variant alleles of two or more genes. Applied Biosystems teaches numerous computer programs which are sold with the DNA analysis system, for example.

Examiner's Answer, page 7. Similarly, with respect to Perkin Elmer, the examiner reasoned that

> Perkin Elmer provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. First, Perkin Elmer teaches the GeneAmp PCR Reagent Kit with AmpliTaq DNA polymerase. . . . This kit provided by Perkin Elmer contains reagents which allow for detection of variant alleles of two or more genes.

Id., page 9.

Appellant argues that "the Examiner has ignored [certain] claim elements entirely i.e., reagents **sufficient** to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the specified group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ. . . . It is a matter of simple fact that the 1993 Applied Biosystems Product Catalog is insufficient, standing alone, to detect the alleles of the perioperative genomic profile kits of the present invention without more, i.e., specific reagents to do so." Appeal Brief, page 24. See also Reply Brief, page 11 (arguing that Perkin Elmer does not teach kits comprising parts that are "sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from" the recited genes).

We agree with Appellant that neither Applied Biosystems nor Perkin Elmer disclose the kits defined by instant claims 72 and 106. As Appellant points out, the claimed kits must include reagents (or component parts) "sufficient to detect" variant

alleles in at least two of the recited genes. We agree with this interpretation of the claims.

None of the kits disclosed by either Applied Biosystems or Perkin Elmer include reagents that are specific to any of the genes recited in claims 72 and 106. The kits disclosed in the references contain reagents for performing a polymerase chain reaction (PCR) process or for carrying out DNA sequencing. Granted, the kits disclosed by the references would allow a skilled worker to amplify and sequence any given DNA fragment, given primers specific to the desired fragment. What is missing from the references, however, is a disclosure of primers specific to any of the genes recited in claims 72 and 106.

"[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Applied Biosystems does not disclose a product meeting all the limitations of claim 72 and Perkin Elmer does not disclose a product meeting all the limitations of claim 106. We therefore reverse the rejections based on Applied Biosystems and Perkin Elmer.

4. Obviousness

The examiner rejected claims 106 and 107 under 35 U.S.C. § 103(a) as obvious in view of either Rosen[3] and Ahern[4] or Tarkowski[5] and Ahern. The examiner noted that "Rosen teaches [that] genotyping of selected loci of the TNF-alpha and TNF-beta

[3] Rosen, U.S. 2002/0119468 A1, published August 29, 2002
[4] Ahern, "Biochemical, reagent kits offer scientists good return on investment," The Scientist, Vol. 9, p. 20 (1995)
[5] Tarkowski et al., "TNF gene polymorphism and its relation to intracerebral production of TNF α and TNF β in AD," Neurology, Vol. 54, pp. 2077-2081 (2000)

coding regions was performed by PCR amplification and restriction digestion," (Examiner's Answer, page 11) and that "Tarkowski teaches analyses of TNFalpha and TNFbeta gene polymorphism[s]," using PCR and restriction enzyme digestion. Id., page 13.

The examiner acknowledged that neither Rosen nor Tarkowski discloses packaging the TNF-specific reagents in a kit, but relied on Ahern to suggest that limitation: "Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come[ ] prepared." Examiner's Answer, pages 11 and 13.

The examiner concluded that it would have been prima facie obvious to package the reagents taught by Rosen into a kit because Rosen "teaches mutations at –308 [of TNF-α] and aa13 and aa26 [of TNF-β] which are associated with predisposition to liver rejection." Id., page 12. Similarly, the examiner concluded that it would have been obvious to package Tarkowski's reagents in a kit because "Tarkowski specifically teaches two polymorphic genes which are associated with AD [Alzheimer's disease]." Id., page 13.

Appellant argues that the examiner's rejection should be reversed because, among other things, the cited references do not provide a sufficient suggestion or motivation to combine their teachings. See the Reply Brief, pages 13-15 and 17-19.

We agree with Appellant that the references relied on by the examiner do not support a prima facie case of obviousness. "[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior

art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted). "[T]he 'motivation-suggestion-teaching' test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims." In re Kahn, 441 F. 3d 977, 988, 78 USPQ2d 1329, 1337 (Fed. Cir. 2006).

In this case, the examiner has not adequately explained why a person of ordinary skill in the art would have been found it obvious to package the reagents taught by either Rosen or Tarkowski into a kit that would meet the limitations of instant claim 106. Rosen teaches a method of identifying organ donors having livers less likely to be reinfected by hepatitis C virus (HCV). See ¶ 0007. Rosen teaches that the TNF-α gene has a polymorphic position at –308: the allele TNF308.1 has a G at this position while the allele TNF308.2 has an A. See ¶ 0035. Rosen also teaches that "[k]nown TNF-β polymorphisms include the TNFc locus, the aa13 locus, the aa26 locus and the NcoI locus." See ¶ 0028.

Rosen amplified and sequenced polymorphic positions in the TNF-α and TNF-β genes and found that livers from donors with the TNF308.2 allele in the TNF-α gene were reinfected by HCV more often and more severely than livers from donors with the TNF308.1 allele. See ¶ 0066. By contrast, "[t]here was no correlation between the TNF-β alleles and time to recurrence, severity of recurrence or the prevalence of rejection." ¶ 0067.

Thus, Rosen teaches that a polymorphism in the TNF-α gene is informative in predicting which livers are more likely to be reinfected in HCV-infected patients, but that polymorphisms in the TNF-β gene are not. In view of Rosen's teaching that TNF-β-specific primers are useless for predicting likelihood of HCV reinfection, we conclude that the examiner has not adequately explained why Rosen would have led a person skilled in the art to package primers specific for both TNF-α and TNF-β into a kit.

Like Rosen, Tarkowski teaches PCR primers for amplifying parts of the TNF-α and TNF-β genes. See pages 2078-2079. Tarkowski analyzed the association between aspects of Alzheimer's disease (AD) and polymorphisms in the TNF-α and TNF-β genes, but concluded that "the levels of these cytokines did not differ significantly in patients displaying different alleles of the TNF gene." Abstract. See also page 2080, right-hand column, second full paragraph:

> [T]he frequencies of TNFα1 versus TNFα2 alleles did not differ between patients with AD and control subjects, suggesting a lack of association between TNF polymorphism and the susceptibility for AD. The intrathecal TNFα levels or the degree of cognitive deficit did not differ significantly between the groups of AD patients with different TNFα or TNFβ gene polymorphism, suggesting a lack of association between TNF polymorphism and the clinical severity of AD.

(Emphases added.)

Thus, Tarkowski teaches that the TNF-α and TNF-β polymorphisms that were examined were not associated with either the susceptibility to or the clinical severity of Alzheimer's disease in potential patients. In view of this teaching, we conclude that the examiner has not adequately explained why Tarkowski would have led a skilled worker to package the TNF-α- and TNF-β-specific primers disclosed by Tarkowski into a kit.

Other Issue

This application is said to be "a continuation-in-part of co-pending U.S. application serial number 09/613,887" (specification, page 1), which is the subject of appeal number 2006-1560. The claims in that application are directed to a method, rather than a kit, for perioperative screening. The examiner rejected the claims as obvious in view of, among other references, Pharmacogenetics[6] and AAS.[7]

AAS discloses that different alleles of the BChE gene affect patients' reactions to succinylcholine (page 139, left-hand column), that "careful DNA analysis is really the only way to establish individual BChE genotypes" (page 140, right-hand column), that "[w]e have been able to sequence the entire BCHE coding region and consider all the possible structural mutations using PCR amplification" (id.), and that "anesthesiologists need to keep up to date about" the application of molecular biology tests to BChE variants (sentence bridging pages 140 and 141).

Pharmacogenetics discloses that cytochrome P4502D6 (CYP2D6) in involved in mediating drug biotransformation (page 309), including the transformation of codeine to its active form (page 317, left-hand column), and that by combining "rapid and specific PCR-based allele-specific amplification tests . . . [with] XbaI RFLP analysis, about 95 percent of all mutant alleles of CYP2D6 could be identified, allowing for the prediction of over 90 percent of PM [poor metabolizer] phenotypes" (page 314, right-hand column).

[6] The reference is cited as "Pharmacogen[e]tics, Chapter 4, pp. 309-326" in the Information Disclosure Statement received in application 09/613,887 on April 6, 2001 (reference number 202 in the IDS).
[7] La Du, "Butyrylcholinesterase variants and the new methods of molecular biology," Acta Anaesthesiologica Scandinavica, Vol. 39, pp. 139-141 (1995)

On return of this application, the examiner should consider whether the references cited in application 09/613,887, together with the prior art of record, would support a prima facie case of obviousness with respect to any of the claims in the instant application.

REVERSED

Lance Leonard Barry)
Administrative ~~Patent Judge~~)
)
)
) BOARD OF PATENT
Donald E. Adams)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
Eric Grimes)
Administrative Patent Judge)

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XI. CONCLUSION

For the foregoing reasons, Appellant respectfully submits that the Office's rejections of claims 106-125 and 127-191 are erroneous. Reversal of the rejections is respectfully requested. Appellant requests that the Board render a decision as to the allowability of the Claims.

Respectfully submitted,

Dated: August 27, 2009

/David A. Casimir/

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